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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

ROBERT E. GROSS

EDWIN B. DUNPHY

M. M. MELICOW

FRANK H. NETTER

GONADAL FUNCTION AND INVOLUTION IN MAN

Transcription of a Panel Meeting

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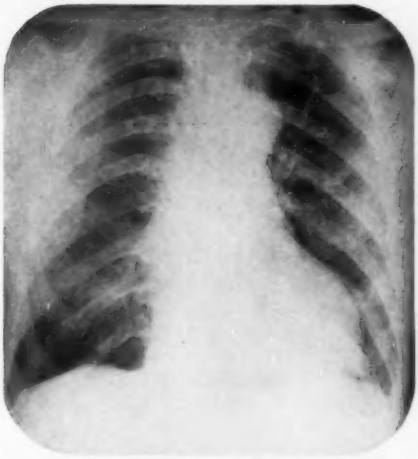

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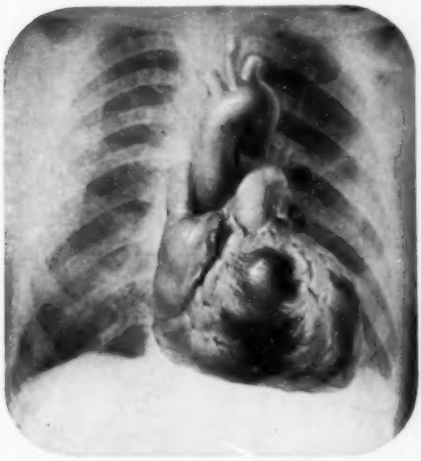

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(1) King, J. W., and Hainline, A., Jr.: Commercial Glucose Oxidase Preparations for the Detection of Glucose in Urine, Cleveland Clin. Quart. **23**:212, 1956. (2) Leonards, J. R.: Evaluation of Enzyme Tests for Urinary Glucose, J.A.M.A. **163**:260 (Jan. 26) 1957.

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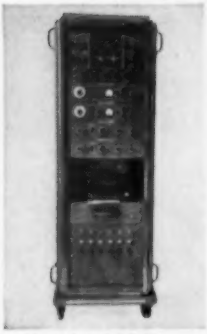

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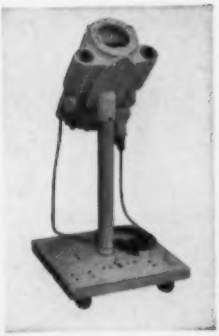

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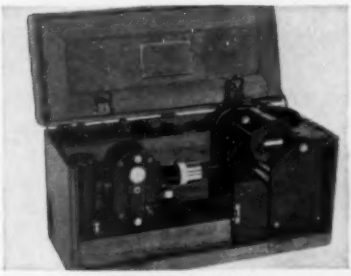

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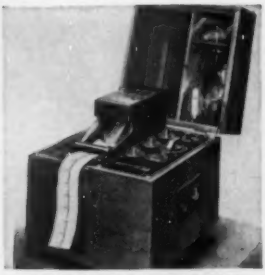

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*Banghart, H. E., and R. K. D. Watanabe: Exhibit Clinical Meeting. A.M.A., Boston, Nov. 29-Dec. 2, 1955.

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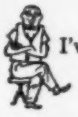
or sitting.  I've belonged to Dr. Phil for ten years now, and he is just as

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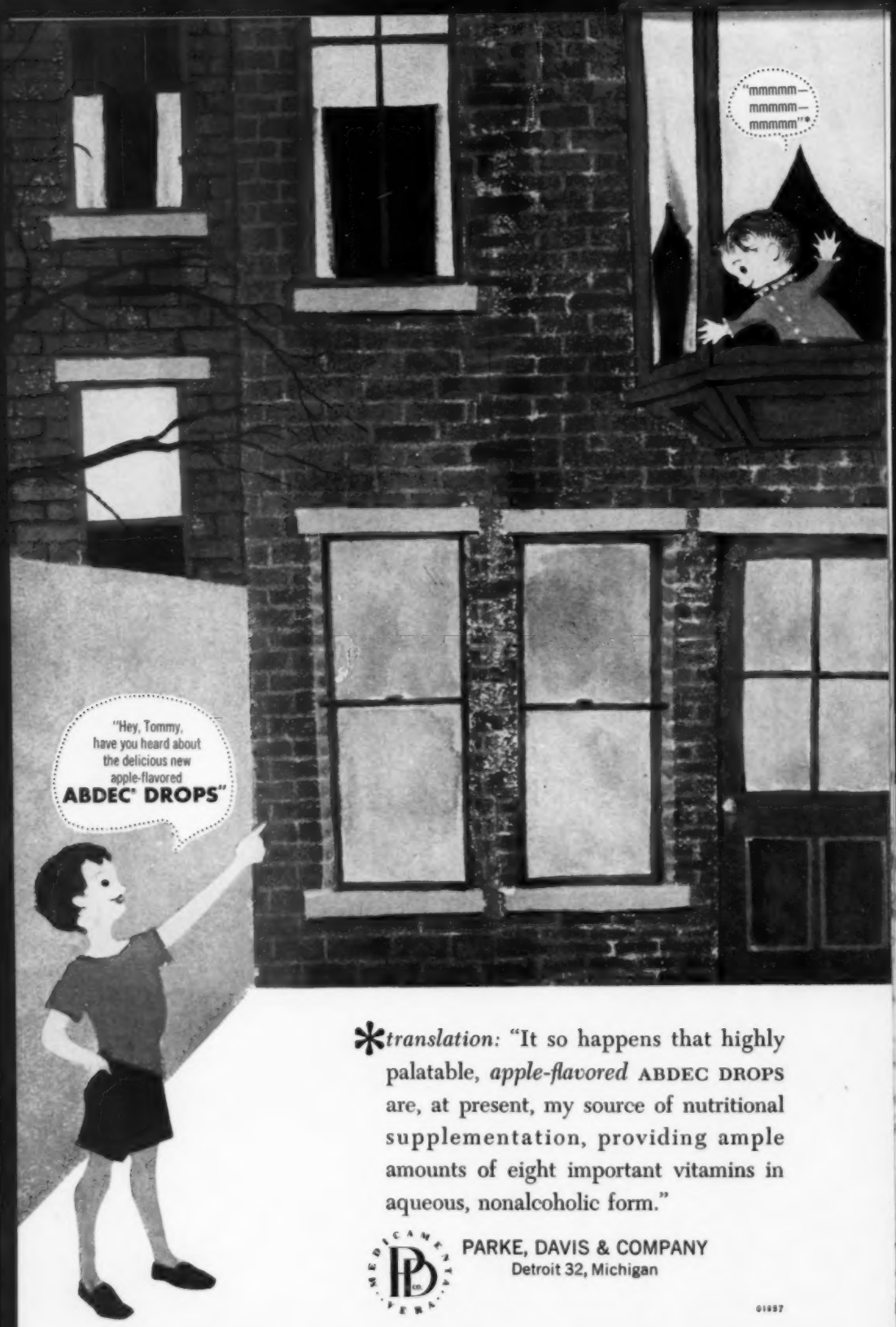

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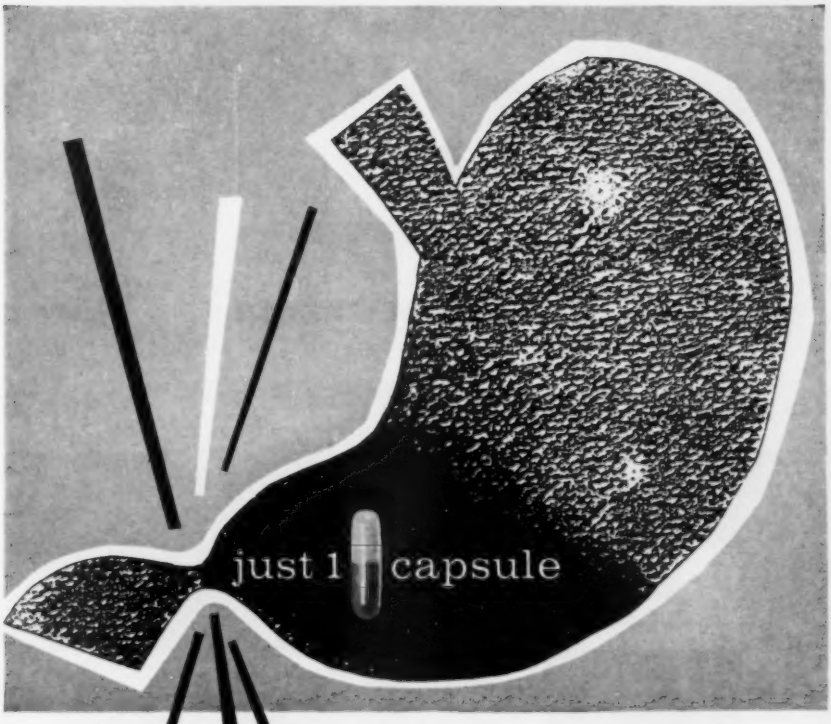

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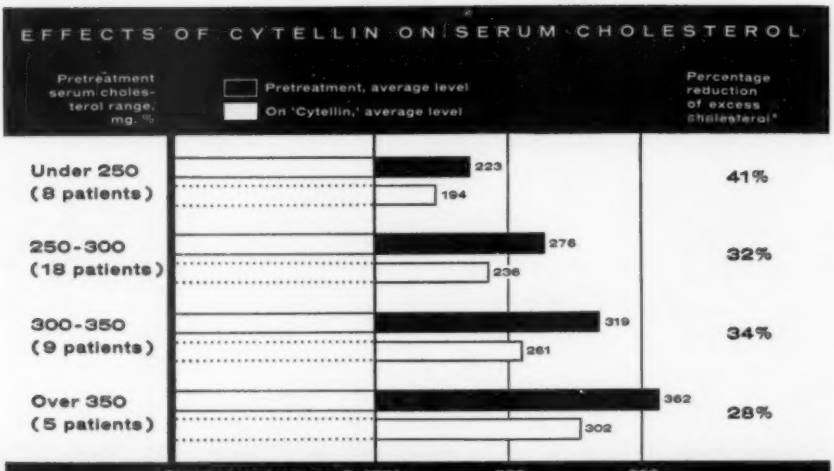

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 33, NO. 5 MAY 1957

PRESENT STATUS OF SURGERY FOR TREATMENT OF CONGENITAL CARDIOVASCULAR MALFORMATIONS*

ROBERT E. GROSS

Ladd Professor of Children's Surgery, Harvard Medical School;
Surgeon-in-Chief, The Children's Hospital, Boston, Massachusetts

THE job of presenting in one-half hour the status of surgery for treatment of congenital cardiovascular defects leaves me in considerable difficulty because it is virtually impossible to summarize adequately all that has transpired in the field during the past few years. It is evident that I can merely touch the high spots, realizing fully that a great body of material must be left unmentioned.

There are nine or ten different congenital malformations of the heart and great vessels for which the surgeon has something to offer in a curative or palliative way; this permits me about three minutes of comment on each condition.

---

* Presented at The New York Academy of Medicine, October 19, 1956, at its 29th Annual Graduate Fortnight.

From the Department of Surgery of the Harvard Medical School and the Surgical Service of the Children's Hospital.

Patent Ductus Arteriosus

Surgery for obliteration of this communication between the aorta and the pulmonary system has long been recognized as being on a firm basis, with an amazingly low risk for the therapeutic undertaking. In a series of slightly over 1000 cases that we have operated upon, the mortality has been a fraction of one per cent. In the average sort of case, the recognition is easy and the surgical treatment has become widely available and satisfactory.

Of increasing interest in the last few years is a somewhat special group of patients with ductal patency in *infancy*. A baby can show a large heart, various signs of failure, and a bizarre picture which is not the typical one which we observe so clearly in older children. It is of great importance to study these infants thoroughly, by catheterization if necessary, for detection of the abnormality because surgical closure of the shunt gives a particularly gratifying result.

Coarctation of the Aorta

The vast majority of humans with congenital blockage in the thoracic aorta, while often symptomless in the first decade or two, will develop in mid-adult life a significant degree of hypertension and some cardiac embarrassment. There is therefore much to be said in favor of excision of the aortic block, and construction of a normal pathway. In some subjects this task is not particularly difficult to perform, but in others it can be extremely exhausting for the surgical team. In spite of the various technical problems which at times arise, we have, in a series of 400 cases, been able to keep the mortality rate down to three per cent.

The surgeon must constantly strive to construct an aortic channel which is of sufficient size. If this cannot be effected by a suitable end-to-end anastomosis of the remaining vessel parts, it is best to introduce some sort of foreign tube to fill the gap. While plastics of various kinds have been employed for this purpose, I feel strongly that properly prepared and preserved aortic homografts give far superior results in the long run.

Tetralogy of Fallot

The tetralogy of Fallot has been treated for some twelve years by shunting procedures, designed to increase the pulmonary flow of blood. Large series of surgically treated cases are now available from various

clinics to indicate what has been accomplished by these procedures, which admittedly are not curative but are of a palliative nature. The shunting operations have stood the test of time in a manner which is rather satisfactory, though of course we do not know as yet what the total life-span of these individuals will eventually prove to be. Complications in the form of cardiac failure or superimposed infection are known, but are not particularly frequent in the picture as a whole. There is certainly vast satisfaction on the part of patients and their families for what has been accomplished in the way of rehabilitation.

With the use of pump-oxygenators which have recently become available and allow open-heart surgery, it might seem that the anastomotic procedures of the Blalock or Potts type are a little old-fashioned, but I feel emphatically that such is not yet true. It is distinctly open to question whether *all* patients with a tetralogy of Fallot (having sufficient symptomatolgy to warrant surgical attack on their problem) should be held back until the *curative* operation, which completely corrects all of the internal defects, carries an acceptably low mortality rate. I think that the anastomotic surgery should still be freely employed, because it can be done with a low risk, with accomplishment of great good, and yet in no way does this step prohibit the use of a curative operation on the heart itself at a subsequent time. However, the fact that Lillehei has recently been able to report 20 recoveries in 29 patients for whom a *curative* operation was undertaken, would seem to indicate that the day is not far off when this more thorough attack on the problem will largely supplant the shunting operations which have attained such a creditable place in our armamentarium since 1944.

Pulmonary Stenosis

Pulmonary stenosis with intact ventricular septum is a good example of what one often finds in the on-rush of medical progress. A lesion which was once thought to be rare, has subsequently been found to be rather commonplace. It was only a dozen years ago that White and his co-workers summarized all of the cases that they could find in the literature—a total of 12. They expressed the feeling that the lesion had little more than academic interest. We all now know that there are many vascular clinics today with long series of these patients who have come to surgery.

The Brock procedure for valvulotomy has been widely accepted, can be carried out with a negligible mortality rate, and while the valve cannot be returned to normalcy, the pressure in the right ventricle can be greatly lowered and the cardiac status thereby improved. There are some who feel that *open* operation and slitting of the valve under direct vision would give superior results, when compared to those where the blind Brock valvulotomy has been done. In spite of theoretical superiority, reports do not appear to show that open-operation has any great advantage over what has been attained by a Brock procedure which has been carefully performed.

There is no clear-cut borderline between those subjects who *should* and those who *should not* have surgical treatment, but when right ventricular pressures are found to be above 100, there is much to be said in favor of surgery, and certainly when pressures are above 150, it should be strongly advised.

Special notice should be directed toward a small group of patients who are brought for therapy after right ventricular failure has developed. Under these circumstances, surgery is dangerous, and it becomes obvious that many tribulations at the operating table could have been avoided if such an individual had been operated upon at an earlier date, when the right ventricular pressure was high and cardiac compensation was good, even though there had been no symptoms at that time.

Interauricular Septal Defects

The repair of interauricular septal defects has now taken an accepted place in the list of procedures which are available for correction of congenital cardiovascular disorders. These openings in the septum are found in a wide range of sizes; there can be no doubt that many of the smaller ones are tolerated through a long life in a reasonably quiescent way. However, when left-right shunts begin to reach such magnitude that the right ventricle is pumping twice as much as the left, surgery is in order. Certainly for those shunts where the right ventricular work is three or four times that of the left, there can be no doubt that a closure of the orifice should be attempted.

There are multiple ways to repair the septum, the details of which are intriguing, but lack of time prevents an enumeration of them here. In general, there are the *open* and the *closed* approaches and, while the

former possesses the advantage of repair under direct vision, experience has shown that closed techniques have been highly successful in the vast majority of cases and can be accomplished with mortality rates which are not over four to five per cent.

Follow-up studies on patients after these surgical repairs have shown complete or nearly complete closure in about 85 or 90 per cent of them. There can be no doubt that some of the very large defects (which were known to be closed at the end of operation) have subsequently been found to be reopened. This emphasizes the point that simple suture-closure under great tension, particularly where the septum is thin, will be attended by failure in some instances. For repair of very large defects, it would be far better to employ the onlay of a foreign material, such as a thin sheet of polyethylene plastic or an Ivalon sponge, accurately sewn into position, since such materials can be placed without any tension on the surrounding suture lines and are known to be well tolerated in the moving heart.

While the closure of an *ostium-primum* defect has been accomplished occasionally, attack on this lesion has been on the whole rather disappointing. Frequently the anomaly has associated shortness of the nearby mitral and tricuspid valves, producing insufficiency of the same, which still leaves a cardiac cripple even though the septum might have been completely closed over. A recent report of Kirklin and co-workers indicates that it is now possible, by open operation, to close the septum completely and also to treat the mitral valve regurgitation.

A distinct contraindication to operation is found in that group of patients—generally in the thirties or forties—whose status is complicated by pulmonary vascular disease, giving reversal of the shunt to a right-to-left direction, under which circumstances operation has been uniformly fatal. This emphasizes the necessity of bringing to surgery those subjects with large left-to-right shunts before disastrous pulmonary complications and reversal of flow appear on the scene.

Ventricular Septal Defects

Ventricular septal defects are extremely common. The smaller ones which have so often been observed in older children and in young adults have widely given the impression that a good many of them are rather benign, excepting for the possible superimposition of Streptococcus

viridans infection, which indeed now has been largely brought under control by the use of antibiotics. However, it is becoming increasingly clear that there are many large ventricular septal defects which are exacting a high toll of life during infancy and early childhood.

The newer methods of cardiac surgery which are now being developed indicate that enterprising surgeons are providing a new and exciting addition to our surgical advance. What has long seemed to be beyond the surgeon's reach has now been shown to be treatable with a high degree of success, notably in the hands of Lillehei and his team in Minneapolis, Kirklin and his staff at the Mayo clinic, and Cooley in Houston, to mention but a few of the leaders. In the Mayo clinic series, repair of ventricular septal defects above the age of two years has given a mortality rate of about 15 per cent. Lillehei's figure is in about the same range; Cooley's is a little lower.

It has already become evident that if pulmonary resistance has risen to a point where the pulmonary artery pressure is about 70 per cent of the systemic pressure, the risks of surgery are high—somewhere in the neighborhood of 50 per cent. We are forced again to recognize that increased success in treating a cardiac lesion will come largely from the surgical handling of the problem before important pulmonary vascular changes have complicated matters greatly. It also becomes increasingly clear that this bugbear of increased pulmonary vascular resistance deserves extensive and intensive research regarding its etiology and therapy if we are to make substantial progress in the future for handling many of the congenital cardiac disorders.

Transposition of the Great Vessels

Transposition of the great vessels which enter and leave the heart is one of the most disastrous anomalies that nature has given to us. The shunting procedures of various sorts, while occasionally providing a modicum of success, have on the whole proved to be rather disappointing. Recently, Baffes has had considerable encouragement with a small group of youngsters by *partial* correction of the abnormality as he transferred the right pulmonary veins and the inferior vena cava into the opposite sides of the heart, employing vein grafts to accomplish this. However, there is considerable reason for doubting whether grafts in the *venous* side of the circulation will remain patent for long periods of time.

Total Anomalous Pulmonary-Vein Drainage

Total anomalous drainage of the pulmonary veins deserves passing mention, because it is being seen with increasing frequency, and it is known that humans with this anomaly seldom live beyond four or five years. Good pathologic studies have shown the various pathways whereby *all* of the oxygenated blood from both lungs enters the *right* side of the heart. From several centers there are now reports, each with a few cases, where surgical treatment has been successful in directing all or most of the pulmonary-vein blood into the left auricle where it belongs, with dramatic relief of symptoms.

Vascular Rings

Finally, vascular rings in the form of double aortic arch or some other configuration of vessels which constricts the esophagus and particularly the trachea, deserve comment. When one of these rings is especially tight, there is literally strangulation of the infant because of great narrowing of the trachea. It is not particularly difficult to open up some portion of such a ring, to give sufficient room for the esophagus and the trachea to grow in a satisfactory manner. These anomalies are not as rare as they were once thought to be, a point which is impressed upon us by the fact that over 100 of them have come to operation in our clinic.

Technical Considerations

Now let us turn from specific lesions to *newer methodology* for facilitating corrective and reparative procedures within the heart itself. Ever since the pioneering work of Gibbon, some 20 years ago, on the development of a pump-oxygenator to bypass the heart and lungs for short periods of time, a whole new vista has been opened up in the field of cardiac surgery. Open operations on the heart bring into the realm of curability many defects which previously were unapproachable or which could only be treated by rather inadequate measures. The work which Gibbon and his wife brought forth fired a great number of investigators in other cities, so that at the present time there are beehives of fever, industry, and research in scores of laboratories, all directed towards the designing of apparatus which can perform the

various tasks in a manner which is safe and satisfactory, and yet does not lead to the production of a monster which is costly to build and difficult to operate. It is impossible here to list all the names and to give commendation which so rightfully belongs to each and every one of these men. Countless ideas have come to the surface and have found expression in the construction of machines of many sorts. The boiling pots of investigation literally seethe with activity. From the brews come a wide range of results, varying all the way from tremendous disappointment to brilliant achievement. The pump-oxygenators being tried on animals, and indeed on humans, can be characterized fairly well as being "hot-rods," for no two of them are similar, and each one has certain ingenuities or devices which have been carefully and paternally introduced by their originators. This makes matters just about as they should be, because the free interchange of ideas and experiences in the surgical literature and at surgical meetings has now permitted us to drop that which is unreliable and to bring into focus those points and principles which seem to promise most in getting us on toward our goal.

All of these workers can be classified as *bubblers*, *membraners*, or *filmers*. The filmers can be subdivided into the *rotating disc* group and into the *stationary grid* enthusiasts.

For the past two years the bubblers have been distinctly in the ascendency, for certainly their machines dominate the picture as far as frequency of employment is concerned. This method of oxygenation has the advantage of giving relatively good gas transference, has delightfully low cost, but leaves something to be desired in that one cannot be entirely sure that all minute bubbles have been removed from the blood before reinfusing it into a patient. This constitutes a real threat in the form of damage to the central nervous system. Tremendous credit is due De Wall, Lillehei, and their co-workers who have indicated that bubblers (with macro-bubbles) have been reasonably effective, even in human cases. They have done much to stimulate all of us in our thinking, even though most of us in the field tend to believe that bubblers will rapidly fall into disuse as other better types of oxygenators are constructed and tested.

As one looks at different kinds of oxygenators, it would seem that the passage of blood through a channel constructed from thin plastic film, allowing oxygen or some gaseous mixture to circulate around the exterior of this, would approach most closely the structural organization

which exists for transference of gases in the human lung. This mechanism has yielded the lowest index of insult on the circulating blood, but it has the enormous disadvantage of inefficiency, since oxygenation is attainable only in that range which is suitable for babies and small children.

The disc filmers have made many types of apparatus, notably the one constructed by Dr. Dennis of New York, who has shown that efficient oxygenation can be carried on even at rather high flow-rates and is accompanied by reasonably low destruction of the blood elements.

In the cards for the future, it would seem that greatest promise lies in the use of a stationary grid or grids, over which blood is made to spread out and flow, permitting good oxygenation, high flow-rate, and a minimum of damage to the blood. Such a machine of the Gibbon-type has been used with amazing success on humans by Kirklin and his confreres at the Mayo Clinic. While enormously expensive, and somewhat difficult to control with the various implements which have been employed to run and monitor it, it now seems that such a mechanism can be greatly simplified, can be built for much less money, and can come safely into the hands of many men throughout the country.

It is quite possible that many cardiac operations can be done without complicated pumps and oxygenators. Riberi and Kajikuri have reported that moderate degrees of hypothermia (30° Centigrade) with periods of venous-inflow occlusion, combined with coronary and carotid perfusion by oxygenated blood from a reservoir, allow repair of cardiac septal defects in dogs with a low mortality. They have observed that such a combination of caval occlusion (with coronary and carotid artery perfusion) could be maintained up to 40 minutes without neurologic sequelae. While this combination has not yet been reported for the surgical handling of ventricular septal defects in man, its extraordinary simplicity and its apparently low risk when employed in animals would certainly warrant an adequate trial in human subjects.

Of considerable interest is the technique of completely stopping a heart during such time as the circulation is temporarily cut off by clamping the cavae, or is carried on by the use of a pump-oxygenator. Abolition of heart-beat can be accomplished very quickly by clamping the ascending aorta and infusing the coronary system with a potassium citrate solution. The heart can be kept motionless for periods, which seem to be safe for 20 or more minutes, while exploration and repair

of its interior are being carried out. At the end of these steps, removal of the obstructing clamp from the ascending aorta allows fresh blood to perfuse the coronary system, and the heart again resumes its rhythmical beating. This technique of wilfully producing cardiac arrest has three advantages strongly in its favor: First, it is somewhat easier to work on the interior of an organ when it is motionless. Second, the danger of producing air embolism from an open heart is greatly minimized. Third, the greatest asset appears to lie in the fact that, for some inexplicable reason, the heart is largely protected from development of heart block which is so apt to occur when interventricular septal defects are repaired while the organ is beating. It is of course possible to raise the legal point that a surgeon who has stopped a heart and cannot get it beating again is guilty of murder, but this is largely an academic consideration, since there is seldom any problem in restoring a heart to activity at the end of a corrective operation.

What about the surgeon in all of this complicated picture? The man who today deals with this type of surgery for the repair of congenital cardiovascular defects has much to think about and is no mere technical expert who patches up a hole in the septum, reams out a narrowed infundibulum, or cuts a stenosed valve under direct vision. Literally, he must constantly have his wits about him, for he must be thinking of many items such as gas-exchanges, acid-base balances, blood clotting mechanisms, blood destruction, optimum rates of blood flow, and yet be ever on the alert to see that the sneak-thief (air embolism) does not somewhere creep in and destroy all of his good intentions and efforts. In a figurative way, this kind of surgeon seems to be riding astride three galloping horses: First, there is the task of repairing a structural abnormality in the central organ of the body, constantly working against the relentless ticking of a clock. Second, there is the management and support of a patient's circulation and oxygenation with a mechanical piece of equipment. Third, in the midst of all this excitement he must, in some miraculous way, remain cool and keep under constant surveillance and control a complicated team of doctors, nurses, and technicians, to make sure that some human error of action does not lead to disaster. To run a show of this sort might seem to be impossible, yet the fact remains that it has been accomplished already in several medical centers, and we are seeing one of the most daring, brilliant, and outstanding chapters ever contributed to American surgery.

Concluding Remarks

Much has been accomplished during the past 18 years in waging a battle for the correction of congenital anomalies of the heart and great vessels. In certain conditions, such as patent ductus, coarctation of the aorta, vascular ring, auricular and ventricular septal defects, techniques have been devised and employed for the total correction of the anomaly, permitting complete restoration of structure and function. For other anomalies, there is today a wide use of palliative procedures which, while not restoring parts to normal anatomy, can greatly improve the patient's status and certainly prolong his life. Already showing clearly above the horizon are bold, new reparative steps accomplishing such things as correcting the tetralogy of Fallot or rerouting the blood when there is total anomalous pulmonary-vein drainage.

It would be very rash to say that in the future, *all* cardiovascular anomalies will be brought under control by surgical means, because at times nature delivers to us some patients with cardiac derangements which are weird and are certainly beyond reach of even the most imaginative repairman. Nevertheless, it is quite reasonable to predict that in the years which lie not very far ahead the vast majority of the common congenital malformations will be treatable with an extremely high degree of success.

NOTICE

Due to greatly increased publication costs, it has become necessary to raise subscription rates of the *Bulletin*.

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RADIOACTIVE ISOTOPES IN OPHTHALMOLOGY*

The Charles H. May Memorial Lecture

EDWIN B. DUNPHY

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I NEVER had the privilege of knowing Dr. May but I've always felt I owed him a great debt. My introduction to ophthalmology was through his remarkable little book, "Manual of the Diseases of the Eye," and also through his electric ophthalmoscope, which was so fascinating to me as a medical student. It would be an exaggeration to say that these were the determining factors which influenced my decision to specialize in this field of medicine but they certainly had a lot to do with it. Therefore, I am particularly honored to be chosen to give the Charles H. May Memorial Lecture.

Although the use of radioactive isotopes in the field of general medicine is not new, their employment by clinical ophthalmologists has never been extensive. This is partly because of the difficulty of obtaining them until relatively recently, and partly because of a not too thorough understanding of the subject on our part. It is the purpose of this lecture to briefly review some of the historical and theoretical background, then to evaluate the role of these substances in our specialty, pointing out their usefulness and their limitations and, finally, to speculate on their potentialities in the field of therapy.

Because I believe this audience is composed chiefly of clinicians, like myself, I am going to review some of the elementary concepts of atomic energy, hoping that, if any nuclear physicist is present, he will be patient, since he will have a so much better understanding of this particular part of the subject than I.

A thorough basic knowledge of atomic energy can be obtained only by considerable study and work under the guidance of a nuclear

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physicist, something which most of us will never find the time to do, but there are certain fundamentals that every clinician must have at his fingertips if he wishes to understand the application of these principles to clinical work.

History

Actually, the atomic theory is an old one,[1] going back to the Fifth Century, B.C., when the Greek scholar, Democritus, taught that all matter was probably composed of small indivisible particles, which he called "atoma." These teachings found little general acceptance however and were not revived to any extent until after the Renaissance in Europe.

For many centuries orthodox scientific teaching had held that matter was composed of four elements: fire, earth, air and water. But doubts began to be raised! Finally, after Lavoissier in 1774 proved that air was not an element but a mixture of gases, and Priestly in 1781 showed that water was made up of two gases, the old four element theory collapsed. Later on, Lavoissier demonstrated 20 separate elements and in 1819, Berzelius, the great Swedish physicist, increased the number to 50. At the present time, there are 103 known elements, each of which is made up of smaller units called atoms.

We now define the atom as the smallest possible or ultimate particle of an element. Thus, the cycle is complete and, after twenty-five hundred years, we return to the original concept of the ancient Greeks!

Modern nuclear physics has now taught us that the atom itself has an internal structure which can be split into sub-atomic particles and, since this fact is responsible for the very existence of isotopes, a brief review of the subject seems desirable.

According to the Rutherford-Bohr model, the atom consists of a nucleus surrounded by a less dense outer shell. The nucleus, which composes 99.98 per cent of the atom, is made up of protons, carrying a positive electric charge, and neutrons, which carry no charge. In the stable atom, the positive charges of the protons are balanced by the negative charges of the electrons, which swirl around the nucleus in various orbits of the outer shell.

The atomic number represents the total positive charge on the nucleus and, since each proton carries one positive charge, the atomic number is equivalent to the number of protons.

The mass number, which approximates the atomic weight, represents

the sum total of the protons and neutrons in the nucleus. Subtracting the atomic number from the mass number gives us the number of neutrons.

Whereas the atomic number determines the chemical nature of the atom, the mass number identifies the structure of the nucleus. For example, when a neutron is added to the nucleus, it does not alter the charge but it does change the mass. Thus, there may be two or more substances each having the same atomic number but with different mass numbers and these are called "isotopes." For example, stable phosphorus is P^{31}. Its nucleus contains 15 protons and 16 neutrons. P^{32}, P^{29} and P^{30} are isotopes of phosphorus. They all have the same number of protons and electrons, they behave essentially the same way chemically and biologically but, because of a disproportion in the normal neutron-proton ratio, their nuclei become unstable and disintegration takes place with release of energy and radiation.

Although naturally occurring radioactive substances, such as uranium and radium, had been discovered just before the turn of the century, it was not until 1934 that Irene Curie and Frederick Joliot found that various stable elements could be made artificially radioactive by bombarding them with certain particles, such as deuterons, neutrons, protons, alpha particles, etc. With this knowledge, a whole new field of medicine opened up in respect to the investigation of physiological processes and the diagnosis and treatment of various conditions.

After a radioactive isotope has been created either by the cyclotron or in the nuclear reactor, it will exhibit a characteristic behavior pattern which is very important for us to understand if we wish to use it intelligently.

The things we must know are the type of radiation emitted, the energy of the rays, and the physical and biological half-life of the isotope itself. Also, we must be familiar with the proper dosage and the radiation hazards not only to the patient but to handling personnel.

Most isotopes emit either beta or gamma rays, or both; only a few emit alpha rays. Alpha rays, which are the nuclei of helium, have very weak penetrating power. Beta rays, which are high speed electrons, are more penetrating. Gamma rays, which are part of the electromagnetic spectrum, are so penetrating that several centimeters of lead are necessary to block them. All these rays may give rise to ionization and photographic effects.

The energy of the radiation depends upon the velocity *and the mass* of the particle ejected from the unstable atom. This is closely related to the degree of penetrability and ionization in tissue and can vary greatly with the particular isotope employed. For example, the beta rays coming from radioactive sulphur can be stopped by less than a millimeter of tissue and, hence, are difficult to detect *in vivo*. Beta rays arising from radioactive phosphorus (P^{32}) have a maximum range of 7-8 mm. and, thus, are very desirable for studying concentrations in the eyeball. Radioactive potassium (K^{42}), on the other hand, has penetrating beta rays of almost 20 mm., along with some gamma rays. Therefore, it is often useful for studying concentrations in deeper lesions of the body.

The half-life of any isotope is the time period in which half of its atoms will have disintegrated. This will vary from less than a second in some of the artificially produced ones to a million years in some of the naturally occurring ones.

From a practical standpoint, the half-life must be long enough to permit the completion of the test but not too long because of undesirable total body radiation if it is to be injected intravenously. Fortunately, most isotopes are excreted rather rapidly, so that their biological half-lives are shorter than their physical half-lives.

For the detection of radioactivity some sort of ionization chamber or Geiger-Muller counter is utilized. The Geiger-Muller tube is the most widely used type, particularly for counting beta radiations.

Another type of detecting device is the scintillation counter, which makes use of the capacity of certain crystals to scintillate when stimulated by ionizing radiations. This method is usually used for the measurement of gamma radiations.

With this very brief summary of the theoretical considerations, let us now see what uses have been made of these radioactive substances in our own field of ophthalmology. These can be discussed under three general headings: 1) physiological experiments; 2) diagnostic applications; 3) therapeutic possibilities.

Physiological Experiments

Many important experimental studies have been performed during the past 15 years in which tracers, particularly radioactive sodium (Na^{24}), have been used to gain knowledge of the circulation of the

aqueous. Because sodium does not enter into cellular metabolism nor concentrate selectively in any tissue to the same degree as phosphorus, potassium or iodine, it lends itself readily to studies of circulation times and fluid transfer. Its half-life of only 14.8 hours restricts its use to short time experiments.

In 1942, Kinsey and associates,[2] in a series of papers, studied the rate of accumulation of sodium, chloride, and phosphorus in the anterior chamber of the rabbit by using the radioactive isotopes of these elements (Na^{24}, Cl^{38}, P^{32}).

They found that Na and Cl appeared to enter the anterior chamber at a rate equivalent to 4 c. mm./min. of whole aqueous in contrast to the 50 c. mm./min. reported previously for water by the same authors. In previous work,[3] using heavy water as a tracer, they had shown that water in the anterior chamber exchanges with that in the blood stream at a rate greatly in excess of the so-called rate of formation of aqueous. This led to the suggestion that the rate of formation of aqueous was more directly related to the movement of substances other than water, e.g., electrolytes.

During the next few years, numerous other investigators, such as Visscher and Carr,[4] Scholz, Cowie and Wilde,[5] Barany and Kinsey,[6] Palm,[7] Duke-Elder, Davson and Maurice[8] corroborated and elaborated on this pioneer work, using Na^{24} for the most part. As a result of all these investigations, it became possible to establish two important concepts which are generally accepted today and which completely changed our ideas on aqueous formation:

1. A secretory mechanism exists in the ciliary body and ultra-filtration plays only a minor role in aqueous formation.

2. The non-electrolytes enter the anterior chamber by diffusion, whereas most of the electrolytes enter by secretion.

Other important studies with isotopes may be mentioned briefly:

In 1949, von Sallmann, Evans and Dillon[9] devised a method of obtaining topographic information of tracer atoms within the individual structures of the eye, using radiosodium (Na^{24}) and taking advantage of the photographic effect of the radiations emitted. By placing frozen slices of ocular tissues on radiosensitive emulsions, they demonstrated that the regions of the ciliary body and optic nerve were the main portals of entry for sodium into the eye from the blood.

In 1950, Potts and Johnson[10] used various tracer substances (Na^{24},

P^{32}, Cs^{134}, I^{131}) to evaluate the role played by the limbal circulation, the tears, and the aqueous in the nutritional supply of the rabbit cornea. The rates of their appearance in the cornea after both systemic and local administration were obtained. It was shown that the limbal plexus played the predominant role in delivering the tracers to the cornea.

In 1951, von Sallmann and Locke[11] reported the results of their experiments with radiosodium and other indicators in the rabbit eye at various periods following irradiation with 2000 R. They demonstrated an increased permeability of the blood-aqueous barrier up to six weeks after irradiation but thought this did not play an integral part in the pathogenesis of radiation cataract.

So much for some of the experimental studies, which have added greatly to our knowledge of the physiology of the eye. There are many others but time does not permit me to relate them here. Let us now consider the value of radioactive isotopes in the field of ophthalmic diagnosis.

Diagnostic Applications

For some years, it has been known that malignant tumors take up phosphorus, potassium and other cell ingredients to a greater degree than do normal tissues. This fact has led to the employment of the radioactive forms of these elements and the measurement of the radiations emitted by the suspected lesion. Without discussing the actual technique of the test, I want to emphasize certain points which seem to me especially important, based on my own experience.

Radioactive phosphorus (P^{32}) first used for intraocular tumor detection by Thomas, Krohmer and Storaasli[12] four years ago, has continued to be the isotope of choice because of certain well-known advantages. By radio assay, it has been shown to concentrate more in the ciliary body, choroid and retina, where most tumors are situated, than in the non-vascular tissues or intraocular fluids. It is a pure beta ray emitter whose rays have a maximum penetration of 7-8 mm. in tissue. Hence, a Geiger counter applied in close apposition to the sclera will be counting only those rays coming from the directly underlying tissues and not those from other parts of the eye or the orbit. It has a convenient half-life of 14.3 days so that readings can be taken on successive days if desired. Also, this precludes the danger of excessive total body radiation from average doses. Last and most important is the fact that it is

retained longer by malignant melanomas than by normal choroid, iris, or ciliary body and, hence, may be expected to give increased counts over the area of the tumor because of increased uptake by rapidly metabolizing tumor cells. Serous detachments of the retina, degenerative lesions, vitreous hemorrhage, and benign iris tumors do not show this increased uptake. Unfortunately, large inflammatory lesions do, but these can usually be differentiated clinically and, furthermore, they tend to lose this increased concentration by the next day.

While P^{32} seems to be reliable in detecting malignant melanomas situated in the anterior and equatorial region of the eyeball, it has certain limitations which must be borne in mind, otherwise erroneous interpretations will be made.

1. Tumors in the posterior segment, inaccessible to the close application of the Geiger counter, cannot be expected to give significantly increased counts. It must be remembered that P^{32} has a maximum range in tissue of only 7-8 mm. Actually the half-thickness penetration is only 2-3 mm. Therefore, it is imperative that the counter must be very close to the lesion to pick up the extra radiations. Unless this is done, a negative test means nothing.

2. When the counter is placed over an extraocular muscle, particularly the medial rectus, the reading is higher than when placed over the sclera alone, due to increased selective uptake by muscle tissue. Therefore, whenever possible, the area of the muscles must be avoided. It is even justifiable to detach the muscle if necessary to complete the test.

3. Because it has been shown that a malignant tumor tends to retain P^{32} longer than normal tissue, the interval between the injection and the counting should be at least 24 hours. Counts taken shortly after injection, when the P^{32} is still diffusing out of the blood stream, will vary tremendously even in different quadrants of a normal eye and, in my opinion, are not reliable. The chance of a good differential between normal and abnormal tissue is infinitely better after a lapse of at least 24 hours, when the concentration in normal tissue has fallen off rapidly.

Most of us working in this field agree that the detection of retinoblastoma by P^{32} has proved unsatisfactory *in vivo* and, yet, when such an eye is enucleated and the Geiger counter applied directly over the tumor a high count is obtained compared to other quadrants of the same eye. No satisfactory explanation for this has been advanced. Incidentally,

it should be mentioned that there are some hazards to using P^{32} in very young children because of its concentration in the immature blood forming organs.

Besides P^{32}, other isotopes have been employed for diagnostic purposes. Trevor-Roper, Newton and Nicholson[13] of England reported unsatisfactory results with I^{131} (diiodofluorescein) in the detection of intraocular malignant melanomas. Apparently this isotope was employed to overcome the inadequacy of P^{32} for detecting lesions in the posterior part of the eyeball. However, I^{131} is chiefly a gamma ray emitter whose deeply penetrating rays coming from back of the eye will obscure the picture by masking the counts coming from the tumor itself. The same objection can be brought against radioactive potassium (K^{42}) and radioactive rubidium (Ru^{86}), which have been employed recently. These isotopes emit both beta and gamma rays and it was hoped that in large posterior tumors they might give rise to sufficiently increased counts over the involved eye to be of diagnostic significance. Such is not the case, however, in my experience.

It would appear, therefore, that up to now nothing has been found superior to the short range beta particles of P^{32}, in spite of its obvious disadvantages in posterior lesions. This is not due to any fault of the isotope but to lack of adequate Geiger counters that can be placed behind the eyeball.

In the diagnosis of certain adnexal malignancies, P^{32} is said to be of value. Bauer and Steffen[14] report that malignant melanomas of the skin can be differentiated from benign nevi by significantly increased concentrations of this isotope, but basal cell and squamous cell carcinomas cannot be differentiated with any degree of accuracy. Terner, Leopold and Eisenberg,[15] on the other hand, using different criteria for positivity, feel the test is valuable in diagnosing these lesions. The discussion is somewhat academic because most lid lesions are accessible to biopsy and excision.

Therapeutic Applications

In the field of therapy relatively little has been done in ophthalmology, comparable to the accomplishments in other fields of medicine, because of the risk involved in damaging delicate ocular structures. However, some of the attempts which I shall mention are extremely interesting and suggest hopeful possibilities for the future.

There are four ways in which a radioisotope might be used for its therapeutic effect:

1. Intravenous injection with metabolic localization in the lesion.
2. Direct injection into a deeply placed lesion.
3. Local application to an external lesion.
4. Employment of certain substances which capture slow neutrons.

According to Low-Beer,[16] the object of all radiation therapy is the destruction of certain tissues and the preservation of others. This is not always possible where a radioisotope has been injected intravenously. When once introduced into the system, radiation cannot be stopped and the effect on all body structures must be taken into account. The ideal situation would be the metabolic localization of some substance in the eyeball similar to iodine ^{131} in the thyroid. Unfortunately, no substance has been found which is taken up selectively by ocular tissues and, even if one were available, the danger to all the normal ocular structures would be great, if destructive doses were used.

Terner, Leopold and Eisenberg[15] have pointed out the possibility of achieving therapeutic concentrations in ocular tissues with the initial employment of x-radiation followed by the intravenous injection of a radioisotope which would concentrate in tumor tissue. This idea is based on the work of Ashkenazy, LeRoy, Fields and Davis,[17] who showed that the uptake of radioactive substances in previously irradiated tissues was greater than in non-irradiated similar tissues. One wonders if this would be practical in the eye, since a delicate balance would have to be struck between a destructive concentration in the tumor and a non-destructive concentration in the normal ocular tissues, which had also been subjected to x-radiation and, therefore, would presumably show an increased uptake also.

Direct injection offers greater hope of success and a number of attempts have been made to destroy ocular tumors and other lesions by this method, using various radioisotopes.

Moore, Stallard and Milner[18] of England in 1931 apparently were the first to plant radon seeds directly into a retinoblastoma, although many other attempts to irradiate these tumors by x-rays, and by radium needles placed in the orbit, had been made previously by others. Reports on the success of implantation of radon seeds have been variable. Recently Joyce and Scott[19] of Australia have reported a method of treating intraocular melanomas and retinoblastomas by sewing radon

seeds, cut from capillary gold wire, into the sclera directly over the tumor, after carefully measuring and localizing it and carefully calculating the dose of destructive radiation required for its size. They report very favorable results.

Trott and Wheatley[20] of England have used radioactive tantalum wire ($_{73}Ta^{182}$) to treat retinoblastomas. This is a gamma ray emitter with a half-life of 111 days. The wire is threaded through a polyethylene tube, heat sealed at each end, which is sewed to the sclera over the tumor area.

Another dramatic use of radioactive tantalum ($_{73}Ta^{182}$) has been reported by Lloyd and Ellis[21] of England to attack a rapidly growing inoperable melanoma of the base of the iris. Two needles, containing the tantalum wire, were passed across the anterior and posterior chambers in the region of the tumor, one behind the iris and the other in front of it, coming out at the opposite limbus. The needles were left in place for 30 hours and then removed, the approximate radiation dose to the tumor being between 4,000 and 6,720 R. The tumor did not shrink but three years after the operation it had not grown larger. An opacity of the lens, present before therapy, increased somewhat as might be expected.

Local injection of a colloidal suspension of a radioisotope into a tumor area so that most of the material will be retained near the injection site has been employed in other fields of medicine; for example, colloidal gold ($_{79}Au^{198}$) has been introduced into certain body cavities; and chromium phosphate, containing insoluble radioactive phosphorus, has been used with some promise of success in mammary carcinoma of mice but neither of these methods hardly seem applicable to the eye.

An ingenious attempt was made by Shaffer[22] to destroy a recurrent epithelial cyst of the anterior chamber, occurring after cataract extraction by direct injection of a small amount of astatine ($_{88}At^{211}$) into the cyst. Astatine 211 has a half-life of only 7.5 hours, emits short range alpha particles of relatively high energy, which are stopped by 100 micra of tissue. It was felt that this might be just enough to destroy the cyst wall, without damaging contiguous structures. Unfortunately, it was not successful in this particular case but the idea is an interesting one and suggests possibilities for the future.

Radioactive cobalt ($_{27}Co^{60}$) may prove to have a limited usefulness in ophthalmology. This is chiefly a gamma emitter of five years half-

life which has been used with success by the urologists in treating carcinoma of the bladder and prostate. I have used cobalt 60 in one case of retinoblastoma in which, following enucleation, pathologic section showed the cut end of the optic nerve involved. Since irradiation of the socket in such cases is usually unsuccessful, the orbit was re-explored, the optic nerve located with some difficulty, and three fine cobalt needles were threaded down through the end of the nerve toward the optic foramen. These were left in place for 48 hours and then removed, the calculated radiation dose being about 4,000 R. Unfortunately, this attempt was not successful and cerebral involvement occurred later but I think the idea should be pursued. Reese has already used the same method by planting radon seeds in the nerve stump.

Surface application of P^{32} has been tried by Low-Beer[16] for various superficial skin lesions, such as basal cell carcinomas, hemangiomas, and various forms of verruca, any of which may occur on the eyelids. Blotting paper of known dimensions, soaked in measured amount of radioactive sodium phosphate solution and dried, is applied to the area by adhesive tape. While this method is effective in extremely superficial lesions, it does not influence the deeper ones and, in the opinion of most radiologists, has no advantages over ordinary x-ray therapy with proper shielding of the eye.

For a number of years, beta radiation from a variety of applicators has been used for various superficial ocular lesions. The source employed has usually been radium or two of its degradation products, radon and radium D. More recently, strontium 90, a pure beta ray emitter has been used. The advantages and disadvantages of these applicators have been comprehensively reviewed by Ham,[23] Hughes,[24] Merriam,[25] von Sallmann, Munoz and Drungis,[26] Cogan and Donaldson,[27] and others who have studied the effects of beta radiation on rabbit and human eyes and have determined approximately the minimum cataractogenic dosages. From this work, we know that all of them, except perhaps radium D, can produce lens changes unless great caution is employed. The threshold seems to be lower when the applicator is applied over the limbal area than over the center of the cornea. Undoubtedly this method of beta radiation for superficial lesions has its place in ophthalmology. It has proved most useful in vernal catarrh, recurring pterygia, small benign superficial tumors of the lids and early corneal vascularization. However, those most familiar with it have made a plea for conservatism

because of the late effects that are beginning to show up.

The fourth possible therapeutic application is the use of slow neutrons and their effect on boron. It has been known for some years that when the element boron is bombarded by slow neutrons, the boron nucleus captures a neutron, becomes unstable, and emits alpha particles, which can produce ionization and destruction of tissue.[28] Sweet and Javid[29] have experimented with injecting boron and glycerine intravenously in brain tumor cases and found that the glycerine, while preventing the boron from concentrating in normal brain tissue, did not prevent its increased uptake by tumor tissue. Thus, bombardment of the area with slow neutrons tended to destroy the local tumor without disturbing too much the normal brain. The application of this principle to the eye has never been tried and its effects would be problematical. Theoretically, if the appropriate amount of boron could be injected into an ocular neoplasm and then be subjected to the slow neutron beam, destruction of tumor from short range alpha particles might occur but this is something to think about for the future.

Conclusions

In this talk I have tried to give some of the background of artificial radioactivity so that a better understanding of its clinical applications might be possible. I have also attempted to review briefly the uses that have been made of the radioisotopes in ophthalmology. The question may now be asked: of how much value have they really been in our field of medicine? In answer, I think we can say that in the realm of ocular physiology they have been invaluable. Because of them, we now know fairly accurately the rate of aqueous formation, and the old theory of the aqueous being merely a stagnant dialysate has given way to the newer concept of secretion and flow.

In the field of intraocular tumor detection, P^{32} has proved a definite aid to our clinical judgment, provided certain limitations are recognized. It would be premature to say that it is infallible even in the anterior lesions until more cases have been studied. It is reasonable to expect that, with the development of better instrumentation, the present difficulties of reaching posterior lesions will be overcome. It is possible that other isotopes may be found to be equally good or even better.

In the field of therapy, with the exception of the beta applicators, the radioisotopes have been disappointing so far, but many unexplored

avenues exist and the next few years may bring results undreamed of at the present time.

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GONADAL FUNCTION AND INVOLUTION IN MAN – AND RELATED PRACTICAL MANAGEMENT

*Transcription of a Panel Meeting**

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MODERATOR EARL T. ENGLE: The theme of this Graduate Fortnight of the Academy of Medicine pertains to problems of aging. In no area of medicine is the process of aging so signally circumscribed and delimited as it is in the reproductive system of woman. The male moiety of the human population shows no such involutional pattern related to a specific decade of life or other chronological control. The steroid hormones of the ovary and the testis which regulate or participate in many metabolic processes of the body likewise show great variance in the pattern of involution during this process of aging. In order to evaluate properly the common qualities and the differences of steroid production of the ovary and the testis it is necessary to examine the biological properties of each.

The ovary and the testis are the conservators of the human race, bearing those germ cells and gametes for release and subsequent union which will ensure the perpetuation of that well known species. The several respective gonadal steroid hormones are essential to reproduction. The other roles of these steroids in metabolic processes either as primary or accessory factors will be discussed later on this forum.

The human female may be unique among mammals in that all the ova (eggs) which she will ever have are present at birth. Since there is no formation of new ova after birth in the human and there is a constant loss of ova by various cytolytic processes from birth on, the time arrives when there are no more ova left. They have all been expended.

(Slide) The first slide shows a section of the human ovary at birth with an abundance of primitive egg cells.

(Slide) The next slide shows the ovary after the menopause in which all the ova have been used up or disappeared and there remains nothing but the characteristic tissue of the old and outworn and atrophic organ. This state of affairs is of a good deal of significance when the production of the ovarian steroid hormones is considered. The doctrine of the "primacy of the ovum" states that all the dynamic processes within the ovary are instigated by the egg cell, mostly under the control of the gonadotropic hormones of the anterior pituitary gland.

The ovum migrates into the genital ridge during fetal life. Under its influence, and only by its presence, the undifferentiated cortical stromal cells form first the granulosa and then the theca cells. Subsequent growth and differentiation bring these cells under the activating influence of the gonadotropins. From the years just before puberty until cessation of

reproductive life, this cyclic activation of the ovarian follicles results in the production of one or more waves of the ovarian estrogens.

As the later years of reproductive life are reached this steroid production becomes attenuated. Ovulation becomes less frequent. The abundant, but not replenished, supply of ova has become exhausted. With no more eggs there is no more estrogen production. With lessened or intermittent estrogen production the well known "feed-back" mechanism is interrupted and the gonadotropic titer is increased. This situation results then in the menopause, which usually occurs within a restricted chronological period, say from about 47 to 50 years of age in most cases. The word "menopause" means just that. It is the last menstruation. The climacteric is an epoch of life in women brought about by the decline of estrogenic hormones which is sometimes beset with clinical signs and symptoms of considerable importance. These factors will be adequately discussed by the next speaker. It is probably true that the menopause, related to a loss of all ovarian ova, is a uniquely human condition.

There is some evidence that most mammals, including our nearest relatives the apes and monkeys, continue to form new ova throughout life. In the rhesus monkey, which has been most carefully studied, ovarian ova are present and menstrual cycles are maintained even into advanced chronological old age. Dr. Gertrude van Wagenen, in Dr. Buxton's department at Yale, who is currently the most experienced observer of these matters in the rhesus monkey, assures me that gray and grizzled multiparas in her monkey colony continue to exhibit the cyclic ebb and flow of estrogen production which, in the monkey as in woman, is dependent on the growing follicle and its dominant egg cell.

Perhaps at this point one might be permitted to depart from observed and documented fact, and to speculate on the significance of these differences between woman and her phylogenetically closest relatives, the apes and the monkeys.

In the long, slow and selective process of human evolution, many new qualities and characteristics developed which were uniquely human. The dominant change was in the complex development of the human cerebral cortex. This intricate neopallium required a longer period for myelination of many nerve fibers and tracts. This resulted in the uniquely human pattern of a prolonged period of helpless infancy requiring constant maternal care. The newborn infants of monkeys and

apes are almost immediately mobile and ambulatory, and become independent of maternal care within a few weeks. Thus it is apparent that in humans, and in the human society, the need of long periods of protection, care and training made it necessary for women to cease reproductive function long before they reached the limits of their life span. In recent years the life span has been enormously extended, with women having a greater life expectancy than men. Thus if there are any physiological deficits set up by the loss of ovarian and steroidal competence, these must be understood and evaluated in terms of the total well-being of the woman during her post-reproductive years.

The Aging Process in the Male: In contrast to our observations in woman, the production of gonadal steroids, the androgens, in man is completely independent of sperm production. We may review from a few slides two or three of these factors.

(Slide) This is a completely normal testis tubule of a man in reproductive life showing the interstitial cells which were thought to be the source of androgen production and the multiplicity of generations of germ cells which result in the production of mature sperm.

(Slide) In this unfortunate circumstance, one of nature's experiments, there has been a complete and congenital absence of the germ cells. The tubules are normal but there are not—in my opinion have never been—any germ cells and yet the interstitial cells are completely normal and androgen production and sexual activity in these cases of hyperplasia are completely normal.

(Slide) This slide illustrates the decline of 17-ketosteroids which begins somewhere right here (indicating) what we consider the flaming vigor of youth and then gradually falls off, but there is a very considerable production even until the very latest decade. The other thing which I must emphasize again and again is the enormous variability between men in these various age groups.

(Slide) Then one turns to look at the diversity of the pattern of the testis in men of these older age groups. These are two men in their middle seventies. The only thing that they had in common was carcinoma of the prostate. But on the right side is a completely atrophic, well fibrosed testis, no sperm production, no evidence of germ cells, no recognizable interstitial cell and androgen production. Here, on the left, however, is a textbook picture of a man's testis, a man in his seventies with complete and full sperm production, good androgen production,

normal interstitial cells. I show this slide, as I showed it to medical students, to emphasize the enormous diversity and variability in gonadal pattern, even with the same age. I should be completely honest, parenthetically, and say that the testis on this side, which is a textbook figure of normality, is from a good minister, and I think he never spoiled his constitution with bad gin; and I tell the medical students that is an indication of right living!

I have emphasized this variability in aging processes. We know now, measured in the reproductive system, the great difference in the calendar years between the female and the male of the species.

Keeping in mind these fundamental biological characteristics which differentiate the aging process between women and men one may then turn to the clinical problems which may develop in the older age groups. To consider these problems, and to suggest methods of clinical management, we have a distinguished panel of experts, and it is my great pleasure and privilege to introduce as the next speaker on this panel, Dr. Charles Lee Buxton, Professor and Director, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, who has long had an active and continuing interest in this field. Dr. Buxton!

DR. CHARLES L. BUXTON: It may be of some significance that when your Chairman and I first discussed the implications of our subject tonight and the part I was to play in it, the first subject which came to mind as a point of departure was the menopause and its implications in the process of aging in the female.

The menopause is rather a surprising sort of a physiological change, and I would like to make every effort tonight to stress the fact that it is physiological and not pathological. I suppose the simplest way to explain this process is to say that it just so happens that in the human female a periodic phenomenon of uterine bleeding occurs beginning in adolescence and continuing until middle age, at which time it stops. Each episode of uterine bleeding of course is really nothing more nor less than a physiological expression of disappointment on the part of the endometrium that all the preparation it has gone through during that cycle for the reception of a fertilized egg has come to naught because no fertilized egg has appeared. The organism, therefore, gets rid of this beautifully prepared nest of tissue and hopefully starts in all over again to prepare itself for that fertilized ovum which, statistically speaking,

so rarely arrives.

Possibly Nature, in its infinite wisdom, has a teleological reason why this function should cease at about middle age in the human female. Possibly the evolutionary process has concluded that it is unwise for the human female to produce babies after middle age and that since this is so the menstrual process is no longer useful and Nature has provided a technique whereby it ceases. The probabilities are that the human is the only menstruating primate in which there is an actual cessation of menstruation and ovulation. There may be a little evidence extant to make us doubt this fact, but so far as we know at present this appears to be so.

Although realization at the time of the menopause of the inability to become pregnant is usually a source of *conscious* relief to most women, the reverse is frequently the case subconsciously. Here is the irrevocable physical expression of the process of aging. This brings irresistibly to a woman's mind a realization that she has fulfilled her reproductive physiological usefulness, that she is no longer young, that she must readjust her approach to life.

Let us not immediately, however, become embroiled in the psychological implications of the menopause, but rather discuss for a minute the organic changes which occur as part of the process of aging. The menopause, after all, occurs as a result of primary ovarian failure. The ovary actually ceases to respond to gonadotropic stimulation, and will no longer fulfill its two basic functions as an egg producer and as a sex hormone producer. Our Chairman[1]* has, on previous occasions and other platforms, elucidated the intimate functional association of these two aspects of ovarian activity, and we do not need to discuss that here. Suffice it to say that following the menopause, eggs are no longer produced and so far as we know there is no longer any sex hormone production. I, therefore, submit the statement that following the menopause the ovary is of no more use to the human organism than is the appendix, and that the ovary at this stage can no more be stimulated to secrete estrogen, than a 50 year old man can be stimulated to race 100 yards in ten seconds. Both are part of the process of aging.

The ovary repudiates its responsibility in producing estrogen and possibly also in producing ova, in numerous different ways. Some ovaries apparently conduct themselves in a fashion which results in a gradual

* References at end of transcript, see page 346.

decline of estrogen production from an originally normal level to practically zero over a fairly long time, in fact, possibly over a couple of years. Other ovaries seem to have the capacity for ceasing this responsibility quite abruptly, and their owner may in one month have a very adequate estrogen production and very quickly thereafter, within a period of another month or two, have practically complete cessation of estrogenic production. Other ovaries seem to have the ability to revitalize themselves periodically and thus estrogen production may almost cease and then briefly recur again periodically in declining amounts, until this rather irregular pattern ultimately ceases after a year or more, and no evidence of further estrogen production can be found.

What are the clinical symptoms of this process of aging in the ovary which results in its senility as a functioning organ, when the rest of the woman may be active and healthy and vital, both physically and mentally? So far as we know at the present time the only symptoms which have actually been proved to occur as a result of sudden or possibly even gradual ovarian deficiency are the symptoms of vasomotor instability such as hot flashes and possibly transitory dizziness and headaches. This, in addition to the amenorrhea which has provided this syndrome with its name, are the only symptoms which in any way have been proven to result from estrogen depletion. The vasomotor instability was thought even as long ago as 1914 by Hoskins and Wheelon[2] to be caused by over-responsivity of the sympathetic nervous system as a result of decrease in or absence of estrogenic activity. In addition to amenorrhea and hot flashes, an extraordinary number of other symptoms have been attributed to ovarian failure simply because women occasionally at this time of life have complained of them. Excitability, weeping, palpitation, depression, fatigue, irritability, constipation, dyspnea, sweating and insomnia are but a few of the symptoms occurring at this time of life which have been attributed by various investigators to cessation of ovarian activity. There has never been any proof whatever that the menopause per se is responsible for any of this extraordinary galaxy. Many attempts have been made to correlate these symptoms with definite physiological changes in the menopausal woman[3-8] without success. The two very definite hormonal changes which occur at the menopause, i.e., decrease or disappearance of circulating estrogen and great increase in gonadotropin excretion, have both been accused of producing the symptoms mentioned above, but there has never been any proof that

such a relationship exists. There is obviously no question but that these symptoms do occur, however, at this time of life, and if not attributable to these hormonal changes then to what may we attribute their origin so that we may obtain some appropriate focal point for therapy? There are possibly two sources for these symptoms, one of which is intimately related from a physical point of view, to the subject under discussion this evening and the other, psychologically related.

We must be constantly on the watch that the symptoms of which women of this age complain and which are so commonly attributed to the menopause, are not actually symptoms of concomitant unrecognized pathological conditions which occur at about this time because this is the age at which common degenerative diseases begin to manifest themselves. Symptoms of these diseases may be parading in the guise of menopausal symptoms while the unsuspected degenerative disease is lurking in the background and actually producing these difficulties. Women patients suffering from hypertension, diabetes, hyperthyroidism, even brain tumor and many other common or bizarre diseases whose symptoms have simulated exactly those frequently attributed to the menopause, have been seen not infrequently by the author and every other physician who has involved himself at one time or another in what might be known as a menopause clinic. It is therefore extremely important to investigate every patient during this stage of life who has incidentally ceased to menstruate, in order to avoid the misfortune of later being presented with the *fait accompli* of a full-blown degenerative disease, the progress of which might have been retarded had it been recognized earlier.

The other source for the many symptoms described above is of course the psychological change which occurs at this time of life, and which has been the subject of song and story for thousands of years. A frequent topic since Old Testament times, the involutional psychologies of the menopause are today a favorite subject for psychiatrists and specialists in psychosomatic medicine. To one who is at best only a barnyard psychiatrist, the explanation of the psychological stress which occurs at this time of life is really a comparatively simple one, and it is not surprising that individuals acquire a lot of somatic symptoms because of the attitude of mind which their education and background and emotional life have led them to develop. It is a time of life when psychological stability is frequently difficult to sustain. Women at the meno-

pause age so frequently develop an exaggerated idea of the misfortunes of the process of aging, simply because their physiological condition suddenly has thrust these thoughts upon them, that they develop unnecessary fears and apprehensions concerning themselves, their environment and their relationships to their families and friends. Add to these factors the additional folklore and gossip concerning the alleged misfortunes of the menopause, and it is really not surprising that women suffer from all sorts of subjective complaints at this time of life. It is quite apparent that the unfortunate symptoms must be treated but it is equally apparent that they must be treated by techniques other than estrogen replacement as a substitute for their loss of ovarian activity. This type of therapy is only a postponement of the inevitable.

This does not preclude the fact that other pathological changes possibly occur as a result of estrogenic deficiency, especially in people who have been deprived of estrogen as the result of surgery or by radiation at an early age. I would like to mention in this connection the possibility that osteoporosis may have as one, but certainly not as its primary etiological factor, cessation of estrogen production and circulation in the organism. This is not the time for an extensive discussion of the problem of osteoporosis since it will undoubtedly be discussed more intelligently and thoroughly by Dr. Jailer, but I think we must assume that osteoporosis is part of the process of aging, undoubtedly aided and abetted by loss of estrogen.[9, 10] We must remember, however, that this condition occurs in males and what is probably more important, that it is impossible to reverse this process by later administration of estrogen, even though a patient may be put into positive calcium balance by this administration. I would make a guess, although I cannot prove this, that osteoporosis may well occur in women who continue to receive exogenous postmenopausal estrogen throughout their postmenopausal years. The occurrence of osteoporosis, however, in a young woman who has been deprived of ovarian function, either surgically or radiologically, is an entirely different matter. This woman really has a physiological need of estrogen because of the pathological deprivation of this hormone at an age when it is supposed to be physiologically present. Therefore, in order to reproduce the physiological characteristics of this age group in terms of estrogen production, it is advisable to carry out estrogen replacement at least until the physiological age of the menopause.

This brings up the subject which is at present causing so much con-

troversy—when, how much, and how long exogenous estrogen therapy should be administered to a woman who is ceasing to menstruate at the age of 45 or 50 or who has ceased to do so. It is our opinion that the human female is so constituted genetically by our evolutionary process that she goes through a physiological change at this time of life which results in a cessation of estrogen production by the ovary. We therefore assume that estrogen is no longer necessary for her health and well-being. We recognize the fact that the sudden cessation of endogenous estrogen, which not infrequently occurs at the menopause, produces vasomotor instability which is sometimes a distressing symptom. When we have become convinced that this symptom is not a symptom of some other aspect of the process of aging such as hypertensive cardiovascular disease for instance, we believe that this symptom may be treated with gradually decreasing doses of estrogen over a period of several months. We see no necessity for continued estrogen administration over a period of years which is so often practiced and advocated elsewhere. It may be asked why should not this continued use of exogenous estrogen be carried out if the patient so desires and if she thinks it makes her feel better. It seems to me there are two answers to this question. One is the possibility of carcinogenesis as a result of prolonged and indiscriminate estrogen therapy, and the other is the simple fact that it is not a physiological necessity.

That estrogens are carcinogenic in the human female has not as yet been proven. Suspicion has been cast upon this steroid as being a factor not only in uterine and cervical but also in mammary carcinoma.[11] Its contribution to carcinogenesis is still speculative. Possibly the most incriminating evidence concerns carcinoma of the endometrium, where it has been shown that prolonged uninhibited estrogen production results in a condition of adenomatous hyperplasia which seems almost imperceptibly to pass through an innocuous zone into the area of malignant metaplasia.[12] Therefore, although estrogen as a carcinogenic steroid is at present in an unclarified status, it is nevertheless under suspicion, and if it is unnecessary to use this drug, are we, therefore, because of this suspicion, justified in using it? Were it a hormone such as insulin, for instance, that is essential to the health and welfare of an individual, the matter should be approached in an entirely different manner; but it actually is not, and therefore, it seems to me, we should withhold the use of this hormone for this purpose until further medical investigation

groups have proven it to be innocent of subversive carcinogenic activity.

The other reason for contraindicating its use following the menopause is, admittedly, a somewhat philosophical one. Nature has arranged matters so that the human female does not need estrogen after the menopause to maintain her mental or physical health, well-being and vitality. It seems to me, therefore, that prolonged estrogen administration is a specious attempt to turn back the clock and to actually assist the patient in an escape from reality. Life from the very beginning is nothing but a process of aging, and it seems to me that one aspect of happiness is a mature realization of, and acceptance of, this fact. If we, as physicians, aid and abet an escape mechanism by trying to help women think they are young when they really aren't, are we actually contributing to their welfare? It is incumbent upon us in every specialty to treat this condition known as the menopause, but let us remember that hormonal replacement therapy is one of the minor and temporary aspects of this treatment.

MODERATOR ENGLE: Thank you very much, Dr. Buxton.

That was a very scholarly and very cautious and conservative statement, which one has come to expect from you.

We have really considered the problems of the female as she advances into middle age and beyond, but there are two sexes in this great human race of ours. We cannot neglect inquiry and consideration of some of the events of aging as it pertains to the reproductive system in man. So we direct our discussion to the presentation of Dr. John Robinson, Associate Professor of Clinical Urology at College of Physicians and Surgeons, Columbia University. Dr. Robinson, would you say a good word about the older age man please?

DR. JOHN N. ROBINSON: It is going to be difficult to continue the scholarly discussion of Dr. Engle concerning the hormonal functions and to present properly the male aspects as compared with the women as described by Dr. Buxton.

Sometimes in a man's life he wonders if he has suddenly become old because he has lost interest in women and life in general, and then he wonders if this is because of any serious disease. These factors tend to upset him emotionally and physically, creating a so-called crisis or male climacteric. It is suspected that up to 30 per cent of men at some time, usually after the age of 40-45, may develop certain symptoms which fit into this category. For the sake of argument, let us assume this situation

exists—how can we tell what part is due to psychiatric problems, what part is due to hormonal imbalance, what part is due to organic disease and what part is due to just fading away?

I would like to review the etiology briefly. The cause of these crises has been thought due to a sudden decrease in male hormonal production. Dr. Engle has pointed out that the peak of production is reached between 20 and 30 years of age. After this, the hormone production shows a gradual downward trend. It is possible that during this steady decline there may be a sudden sharp decrease in production. The symptoms become dominant when this fall occurs. Some workers contend that estrogen is produced by the testis but the proof is weak. It may be that an imbalance is responsible for causing these changes. The development of prostatic hypertrophy or the development of chronic prostatitis may cause these symptoms. Sometimes the latter disease is purely congestive with a markedly swollen prostate and with a large amount of toxic prostatic fluid produced, some of which must be absorbed by the system causing mild or severe symptoms. An early hypertrophy of the prostate may play a part by causing hormonal imbalance. It has been shown that prostatic fluid from the former type of cases, if injected into animals will make them seriously ill.

The symptoms of this malady are vague, develop slowly and insidiously, and often are transient. Because they are so innocuous and usually subside by the time a busy patient is ready to see the doctor, the symptoms are forgotten and the patient never arrives at the doctor's office until symptoms are full blown. They are more noticeable when the patient is at rest rather than during a period of intense physical or mental activity. Other symptoms may be inefficiency, weakness, exhaustion and indifference to work or pleasure. Severe cases often have a loss of memory, irritability, headache, hot flashes, and it is not unusual to find the symptoms related to the male genitalia, the inguinal region or the perineum with a dragging down sensation. It is also common for the patient to have mild urinary symptoms such as urgency, frequency and difficulty in voiding. The sex urge may become totally inadequate. In these problems it is important to determine whether there is a psychologic basis for the above symptoms or whether the crisis starts because the patient is just too busy to have an interest in sex.

The general physical examination is usually normal, but the urological examination may show congestion of the prostate or mild hyper-

trophy. The blood pressure may be low. In other words, there are few physical signs.

Treatment of these people is difficult and it is important to obtain a detailed history to learn their mental and physical capabilities. If any type of fixation is discovered or if there is pain in the testis with no objective findings, careful examination of the prostate and testes is necessary. If on the other hand, the patient has no symptoms pertaining to his urinary tract and we find he is completely normal physically, he must first of all be reassured. He must have the whole situation carefully explained. Then one of the male hormones is administered in adequate doses. I usually find this treatment more effective if given intramuscularly two or three times a week. If it is not possible to give the hormone by injection, then oral administration will sometimes suffice. Vitamin B complex plays some role in these depressive states. Large doses of vitamin B complex will often make the patient feel considerably better.

These patients should also receive sedation on a regular and long term basis. Personal hygiene must be very carefully observed. If the blood pressure is low sometimes one of the amphetamine preparations is of value.

The best method of treatment for prostatic congestion is prostatic massage given two or three times a week until the congestion is reduced when it should be given on a weekly basis until cured. In addition to the massage, one of the most effective forms of treatment is instillations of silver nitrate solution 1:5,000 into the posterior urethra. If pus is present, together with the congestion, antibiotics of choice should be given in addition to the massage. When early hypertrophy of the prostate is found then the same type of treatment is recommended although a complete study of the urinary tract should be done to make sure there is no obstructive prostatic disease which requires surgery. If not, the patients can often be carried along on routine treatment together with judicious use of hormones.

In summary, I have described a vague set of symptoms and their treatment. Whether this is due to a lowered hormonal production, hormonal imbalance, the aging process, or other factors is not known. These symptoms are sometimes called the male climacteric. I know that many can be benefited by adequate treatment of their prostatic condition together with the use of hormones and vitamin B complex.

MODERATOR ENGLE: Thank you, Dr. Robinson, for your exposition

and very cautious appraisal.

Now each of these specialists, one of whom is a specialist in the diseases of women and the other a specialist in the diseases of men, has had his say.

We must now turn to another type of specialist, the internist. It is my pleasure to introduce Dr. Joseph W. Jailer, Associate Professor of Medicine, College of Physicians and Surgeons, who includes in his practice both men and women.

DR. JOSEPH W. JAILER: Many states of ill health have been attributed to the menopause. In addition to the usual symptoms of hot flashes, dizziness, fatigability, and the like, which we have come to describe as the menopausal syndrome, there has been added in recent years the occurrence of postmenopausal osteoporosis. This affects mainly the spine and may or may not be associated with symptoms. Although the internist sees the usual patient with climacteric symptoms, the signs and symptoms of gonadal failure in the female and the male have been discussed by Doctors Buxton and Robinson and, by the way, I would like to take issue with Dr. Robinson on some of his points in the discussion. I shall confine my remarks this evening to those pertaining to osteoporosis, postmenopausal and otherwise.

Osteoporosis is defined as a deficiency of bone arising from insufficient matrix formation, in the presence of normal calcification of osteoid tissue. This is in direct contrast to osteomalacia, which is a softening of the bone; it is a deficiency of calcium or of vitamin D or of both. In osteoporosis, the trabeculae are fewer and thinner than one finds in the normal. It is confined primarily to the lower thoracic and lumbosacral spine. In the spine the centrae shrink and may become depressed, chiefly in the center, giving rise to what has been called the "fish vertebrae" or the "codfish vertebrae." The spine may show a rounded kyphosis and is shorter than normal.

Before one can discuss the pathological findings in the skeletal system one must know more about the life history of the normal or so-called normal skeletal system. It has been estimated that the weight of the skeleton increases from early infancy to reach a peak between 25 and 30 years of age. There is then a gradual fall to the age of 45 when another rise occurs, to reach a second peak at 55 and followed by a steady decline. It is thought that the second peak (at age 55) is probably spurious and is accounted for by the formation of new bone around

articular surfaces, skull and the axial skeleton. In other words, man reaches his peak as far as the skeleton is concerned at the age of 35, and then there is this gradual decline thereafter, which means that the skeleton is losing more calcium each year. The second peak is accounted for by the formation of pathological bone around the articular surfaces.

It must be borne in mind that bone is a dynamic tissue and that at any one time there is a great turnover of the various substances which go into the formation and reabsorption of bone. Some of the factors involved in maintaining the normal constituency of bone are:

A. NUTRITIONAL FACTORS. When the patient does not receive or absorb adequate substances for the growth of bone, pathological changes may occur in bone. These important substances are:

1. *Protein.* Pathological changes occur when there are defects in *alimentation,* when there is *deficiency from starvation* and may also recur when there is *protein loss,* as for example, from nephrotic renal disease, and as may occur in pregnancy, especially in undernourished females. Pregnancy makes a great demand for calcium upon the mother. It has been claimed that osteoporosis has a much higher incidence in older women who have been pregnant, as contrasted to women who have never been pregnant. Nordin and Roper have described four cases of severe osteoporosis in younger women after pregnancy.

2. *Calcium and Phosphorus Intake.* Vurthin-Paulsen studied 33 patients over the age of 68. In this group there were 28 females and 5 males. He was able to find a good correlation between the calcium intake in the diet of these patients and the incidence of osteoporosis. In a careful study of the dietary intake of these patients, he found there was a 74 per cent incidence of osteoporosis in those patients whose daily intake of calcium was less than 500 mg. per day; whereas in those patients whose calcium intake was over 500 mg. per day there was only a 14 per cent incidence of osteoporosis. It has also been found that in the presence of osteoporosis, when the calcium intake is high, patients can be put in positive calcium balance, without any change in protein metabolism.

B. ENDOCRINE FACTORS.

1. *Parathyroids.* Osteoporosis may be found in the presence of hyperparathyroidism. There need not be any cystic areas (osteitis fibrosis cystica) and there need not be any deformities.

2. *The Thyroid Gland.* It is claimed that the thyroid is involved in the occurrence of osteoporosis. However, the role that the thyroid plays

is certainly not clear. Osteoporosis has been shown to occur in long-standing hyperthyroidism, but it must also be borne in mind that many cretins show osteoporosis.

3. *The Adrenals.* Osteoporosis occurs in about 85 per cent of patients with Cushing's syndrome. This is due to the oversecretion of the adrenal corticosteroids, presumably hydrocortisone. It should be remembered too, that osteoporosis has been shown to occur in patients receiving large amounts of cortisone over long periods of time. Presumably the mechanism is due to the anti-anabolic or catabolic effect of these adrenal steroids upon protein metabolism.

4. *The Pituitary Gland.* Osteoporosis has been known to occur in burnt out acromegaly. Whether this is due to the hypogonadism which may occur at this stage, or whether it is due to other factors, is unknown at the present time.

5. *The Gonads:*

The Ovary. The earlier work in chickens and in other birds demonstrated a great effect of the estrogens upon serum calcium and phosphorus. It must be borne in mind that the mechanism of the metabolism of calcium and phosphorus in birds is quite different from what is known to occur in mammals. The calcium is necessary for the deposition of the shell of the egg. Apparently it is stored in the long bones until that time when it is used by the bird for the laying down of the egg shell. In the mouse, hyper-ossification has been described with the administration of large doses of estrogen. In the rat, on the other hand, androgens accelerate ossification, whereas estrogens inhibit it. Consequently, those mechanisms which obtain in one species may not occur in the other. That the lack of gonadal secretion may be a factor in the production of osteoporosis is borne out by the fact that in Turner's syndrome (so-called ovarian agenesis), the incidence of osteoporosis is quite high even in individuals in their early twenties, and the same occurs in various types of eunuchoidism in the male. It has also been thought by Albright's colleagues that the incidence of osteoporosis is much greater in women who have had a surgical or irradiation menopause. However, several recent series have cast doubt upon this contention. In a recent publication, Donaldson and Nissin showed that in their series there was no greater incidence of osteoporosis in those patients who had undergone a surgical menopause than in those who had undergone a natural menopause.

C. MECHANICAL FACTORS are involved in the production of osteoporosis.

1. We are all familiar with the osteoporosis which occurs upon immobilization. It has been shown by Shorr and his colleagues that when normal healthy men were immobilized they went into negative calcium balance.

2. Osteoporosis occurs after injury, especially in the long bones.

3. *Sudek's atrophy—apparently neural.* Osteoporosis bears no specific symptoms. The patient may be completely asymptomatic or, on the other hand, he or she may be completely incapacitated. The pain usually originates in the back and may radiate to the trunk, the buttocks, and down the legs. It is often aggravated by movement or by flexing the trunk. It may be accentuated on sneezing or coughing and be very suggestive of root compression. As for the *signs* of osteoporosis there may be none at all, or there may be gross spinal deformity. The latter results in a shortening of the trunk and a rounded kyphosis.

Pathological fractures occur in postmenopausal osteoporosis. This may occur in many instances as a result of very minor trauma. In fact, it has been claimed that one-third of all pathological fractures in which there was no malignancy was due to osteoporosis. The diagnosis is made in the living state, by x-ray. Many difficulties are involved in making the diagnosis of osteoporosis. The x-ray appearance may be osteoporotic to one radiologist and normal to another. It is purely subjective. It has been calculated that, in order to get a detectable change in the x-ray, approximately 50 per cent of the calcium must be removed from the bone.

Differential Diagnosis: In my opinion osteoporosis is a diagnosis by exclusion. One must exclude multiple myeloma, hyperparathyroidism, Cushing's syndrome, or the exogenous administration of adrenal steroids and malignancy. I recently had occasion to see a 48 year old woman in consultation, in whom the diagnosis of postmenopausal osteoporosis was made. Upon careful questioning I found that her severe back pain actually antedated her menopausal symptoms. Though she had no fever, a normal sedimentation rate, negative Bence-Jones protein, normal electrophoretic pattern of the serum and normal serum globulin, bone marrow biopsy of a very small previously overlooked cystic area in a spinous process revealed the presence of excessive amounts of plasma cells. This was not a case of postmenopausal osteoporosis, but of multiple myeloma.

She subsequently developed a pathological fracture of the neck of the femur and again multiple myeloma cells were found. She died later and at postmortem a diagnosis of multiple myeloma was obvious.

Osteoporosis is about six times more prevalent in the female than it is in the male. In the absence of the diseases mentioned above, it usually occurs after the menopause—called senile or postmenopausal osteoporosis. When it occurs in younger people, it is referred to as idiopathic osteoporosis, cause unknown.

Treatment. According to the concept of Albright and others, osteoporosis is due to a loss of protein from the osteoid matrix with a secondary loss of calcium. Consequently, the rationale of the hormone treatment would be the administration of the estrogens and androgens because of their anabolic effect. He had found that these hormones put the patients into positive nitrogen balance and secondarily into positive calcium balance. The protein content of the diet should be high. The calcium content should also be high in view of the recent findings that a high calcium diet in itself may put these patients into positive calcium balance. Shorr has advocated the addition of strontium to the diet, to further increase mineral deposition.

In many cases, patients do well on this regimen. They become free of pain, they may discard the casts and become useful citizens again. However, very little or no recalcification of bone may show by x-ray. In spite of this, it is well worth treating this condition. Although there is no evidence that estrogen or androgen lack is the cause of postmenopausal osteoporosis, we are probably getting beneficial results from the pharmacological action of these steroids.

The estrogens may cause undesired complication such as uterine bleeding and virilization may occur with the use of the androgens.

I enjoyed these comments by experts and I am impelled to comment on how much endocrinology in medicine has changed since I entered the field 30-odd years ago.

MODERATOR ENGLE: I noted a little controversy developing when Dr. Jailer said he disagreed with Dr. Robinson. I should like to know the area of disagreement.

DR. ROBINSON: I shall try to clarify my position. Whether it is wise to give any male hormone because of the danger of carcinogenesis and because of the vagueness of the male menopausal symptoms is not easy to answer. But on the one hand it is relatively safe and on the other

hand, it does gives some relief.

DR. JAILER: My feeling is that when one arrives at a diagnosis one uses the specific therapeutic agent for the particular disorder. I am very skeptical of the existence of the male menopause as a syndrome. At the Endocrine Diagnostic Laboratory at Presbyterian Hospital we have certainly done gonadotropic assays on urines which have come from the urological service and some from our own service. In the absence of the kind of testicular pathology that Dr. Engle has shown, we have never found elevated gonadotropins which would be an index of testicular atrophy. If it does not exist I would not like to give testosterone.

DR. ROBINSON: There is often no laboratory evidence of malfunction but the patient can still be made more comfortable by medication.

DR. JAILER: That these symptoms exist I will not deny.

DR. ROBINSON: Some men are relieved when they receive male hormones and/or prostatic massage.

DR. JAILER: I would go along with you on the prostatic massage. I would not go along with you on the administration of testosterone or vitamin B. If one has a vitamin B deficiency he should be given vitamin B. The concept of inactivation of hormones by vitamin B deficiency has I think been pretty well exploded. It has been shown that the inability of the liver to inactivate estrogens and androgens in the presence of vitamin B deficiency was due to inanition. The investigators who claimed that it did, did not have paired feeding experiments. One of the papers that we published at that time showed that the rats on a partial starvation diet when given many milligrams of vitamin B, still could not inactivate the estrogen in the presence of inanition. When you fed the animals up they inactivated it.

DR. ROBINSON: Dr. Jailer speaks accurately concerning the laboratory findings but I do not believe that carcinoma of the prostate will develop following a short course of male hormones but if given in larger doses over a long period of time it may predispose to cancer.

DR. JAILER: We have to draw the line somewhere. On the one hand, people are adrenalectomizing patients because of breast carcinoma, because the adrenal is secreting a little bit of estrogen, or for prostatic carcinoma because the adrenal is secreting a little bit of androgen. On the other hand you want to give androgens and estrogens to anybody who is in that age group. I think we have to have some degree of consistency.

DR. ROBINSON: I think symptomatology must be considered.

MODERATOR ENGLE: Is it permissible now at the end of the panel to get up and wander around? I am just an old university professor. I can't stay put all the time. I really have some dillies of questions which have been submitted.

DR. BUXTON: Here is one you dropped on the floor. I don't know whether it was on purpose or not!

MODERATOR ENGLE: That is a very serious one, Dr. Buxton, I am going to give it to you.

What is the opinion of the panel on the advisability of using estrogen hormone cosmetic cream? That is a $64 question.

DR. BUXTON: A lot more than $64 is involved, from what I hear! I think the medical opinion concerning the advisability of using estrogenic hormone cosmetic cream would be that it is probably not necessarily inadvisable but that it is probably useless. There is no particular reason why a small amount of estrogenic hormone cream should not be used by individuals who, like Ponce de Leon, are looking for this elusive fountain of youth. But I doubt very much if it really produces any very definite change following its application. It is absorbed by the skin. If large amounts of estrogenic cream are used for instance in the useless attempt to try to increase breast size, which is a common way of employing it, it is absorbed in sufficient quantities to produce other systemic effects such as hyperplasia of the endometrium and subsequent irregular bleeding and even sufficient estrogen concentration to prevent ovulation. Therefore I would say that its use is not advisable even though in small quantities it may possibly be harmless.

MODERATOR ENGLE: *I had one very long and involved question which was directed to Dr. Jailer and I handed it to him and he can read it and comment on its various parts as he goes along.*

DR. JAILER: I think these are very good questions.: 1. "Would increase of calcium over 500 mg. to prevent osteoporosis predispose to renal lithiasis?" Those patients who have developed renal calcinosis as the result of excess calcium intake were really taking up to 10-12 gm. of calcium a day together with vitamin D, which increased the absorption of calcium. In addition they take Gelusil, which as you know decreases the phosphate absorption and tends to decrease the plasma phosphate which in turn will cause a further rise in calcium.

2. "You made the statement that one should be careful in giving cal-

cium to any patient who has kidneys. Would it help the patient without kidneys?"

No. There is an old Canadian proverb, "What ain't, cain't"!

MODERATOR ENGLE: *Dr. Robinson, you dealt with this question a little in your own private argument with Dr. Jailer but this is specifically addressed to you: "Is there danger of accelerating carcinoma of the prostate by giving testosterone?"*

DR. ROBINSON: The answer is "no" for small doses but for large doses given over a long period of time,—possibly.

MODERATOR ENGLE: *Dr. Buxton, I think this is a very practical point. Everybody wants to have your opinion about this: Discuss the advisability of the use of oral versus injectable estrogens.*

In days gone by Dr. Buxton and I have argued violently on both sides of this question.

DR. BUXTON: I am glad that question was asked because it gives me an opportunity to tee off on one of my favorite dissertations.

MODERATOR ENGLE: That is right. I knew that was what you were going to do.

DR. BUXTON: We have not used estrogen by injection for I guess well over ten years now except for the purposes of comparison and experiment. We have seen no proof whatever that injectable estrogen has any more estrogenic effect than estrogen when given by mouth. If the oral estrogen is of the type which is assimilable by mouth, such as a synthetic estrogen like stilbestrol, or the natural occurring estrogens such as estrone sulfate or ethinyl estradiol, these estrogens when administered by mouth have, as far as we can tell by determination of the vaginal smear, endometrial biopsy, etc., exactly the same estrogenic effect as estrogens when they are injected. Therefore we see no reason whatever from a hormonal point of view for administering estrogens by injection.

There are obviously other reasons for administering medication by injection but they are not hormonal.

MODERATOR ENGLE: *Dr. Jailer, here is a question which has appeared in several different forms on several different slips, which is of general interest: "Is the combination of estrogen and androgen of any value in older people?"*

DR. JAILER: I cannot answer that question. I don't know.

MODERATOR ENGLE: *That is a good answer.*

DR. ROBINSON: It is reported that doses of both androgen and estro-

gen in small amounts are sometimes helpful in this group of symptoms that I have attempted to describe.

MODERATOR ENGLE: *I must push along on this question because as you know almost every pharmaceutical house in these United States makes a tablet containing both estrogen and androgen.*

DR. BUXTON: And some also have progesterone!

DR. JAILER: I don't know what the answer is. I think aside from trying to induce menstruation or stimulating the appearance of secondary sex characteristics in the eunuchoid male, the androgens and estrogens are used primarily for their so-called anabolic effect and there has been a great deal written about the anabolic effect of androgens and estrogens. In all these experiments that have been done, the anabolic effect has always been greatest in those individuals with deficiency of androgens or estrogens. In other words, it was shown if androgen is given to a eunuchoid then you get a very nice positive balance. If androgen is given to a patient with hypopituitarism, this patient goes into positive nitrogen balance. If the androgens are given to a female, you then get a very slight effect on nitrogen balance, and if the androgens are given to a normal male you get practically no effect. So I don't know whether these substances are really effective in the absence of deficiency states.

MODERATOR ENGLE: *Dr. Jailer has voiced one of the earliest, really practicable, applicable laws of endocrinology; an endocrine substance or its active principle is to be administered to repair deficiency, but it was rarely ever additive in the absence of a deficiency. I think that is still one of the fundamental truths of experimental and clinical endocrinology.*

Dr. Buxton, you have just been saying that you literally did not give estrogens but some of your confreres out front didn't believe you. When you, Dr. Buxton, have given estrogen to a postmenopausal patient and have gotten uterine bleeding how do you stop it, assuming that repeated Papanicolaou smears are negative?

DR. BUXTON: I would like to answer the last part of that question first. Assuming that repeated Papanicolaou smears are negative, in a case of uterine bleeding there is no justification for assuming that the individual does not have a carcinoma, either of the cervix or the endometrium. An individual, even though she has been receiving estrogen, who develops uterine bleeding postmenopausally must be curetted

in order to be assured of the fact that this bleeding does not come from a concomitant carcinoma which is present at the same time that you are giving her estrogen. As a matter of fact, that is one of the great inconveniences of estrogen therapy because you never can be sure. This is one of those things about which you must be safe. Therefore an individual who does develop bleeding following estrogen therapy or any woman of postmenopausal age who starts to bleed, no matter what kind of therapy she is receiving and regardless of whether or not she has negative Papanicolaou smears, should be curetted to eliminate the possibility that she may have a carcinoma of the corpus or cervix. If the bleeding comes from excessive estrogen dosage the curettage cures the situation. I should think that it ought to be an indication to the individual administering the estrogen that the estrogen should no longer be given. That would be my answer.

MODERATOR ENGLE: *That is a very adequate answer.*

It is now necessary to bring this meeting to a close. I wish to thank the members of the panel for their interesting and instructive presentations and the audience for its close attention.

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INTER-RELATIONSHIPS OF MEDICINE AND ART*

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There are probably no two professions which on the surface are so unlike as Medicine and Art, but which on closer examination reveal many similarities and interrelationships. They both have had a common origin and heritage. Each requires of its participants many similar aptitudes and interests. Both are engrossed in the study of Man and his environment, and as we trace the development and rise of Medicine and Art throughout the ages we find areas of overlapping between the two disciplines (Fig. 1). Many artists have depicted medical subjects (Figs. 2 and 4) and there have been many physicians who have engaged not only in the art of medicine but also in the arts of painting, sculpture and literature, etc. (Tables I and II). As far as the last is concerned W. Somerset Maugham has said: "I do not know of any better training for a writer than to spend some years in the medical profession."

In ancient society the physician and the artist were parts of a trinity consisting of medicine, art and religion. The man of religion was also a priest-healer, a "medicine man," who not only acted as intermediary between deity and people, but also healed the sick. And the priest-healer was also, in a way, the earliest art patron and critic in history, for he bore the responsibilities of presenting the deity in a concrete art form and of procuring the best available talent to execute images of the gods. Thus the priest was at once the doctor of primitive society and the dictator of the form and content of that society's art. He was often an artist himself (Fig. 3).

During the Dark Ages, medicine and art continued to be part of and to serve religion. The Renaissance brought into existence the scientific approach to problems in every field, including medicine and

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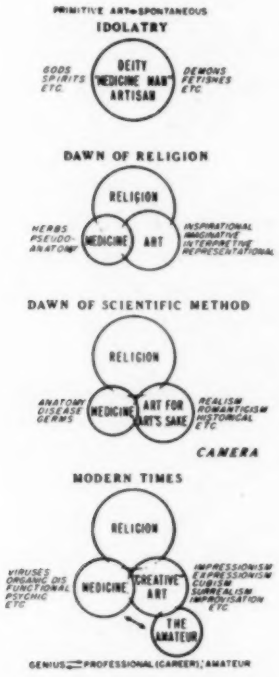

Figure 1—Schematic representation of the evolution and interrelationship of religion, art and medicine. The medicine man of antiquity was a combination of all three. The disciplines are now distinct but there is still some overlapping. The amateur artist is a phenomenon of the modern age.

art. Perhaps the best known product of that method was the mastery of perspective in art (Uccello, etc.). Other problems, especially that of accurately rendering the parts of the human body, required deeper study, and at this point the artist and physician began at once to collaborate and, in some cases, even to co-exist in a single figure. At first, the dissection of the human body was forbidden and physicians were forced to use diagrams of animal bodies and fanciful or imaginative drawings of the human body (Fig. 5). But doctors and artists found their material as best they could. Some became body snatchers from graves, deliberate lawbreakers who hurriedly dissected their subjects under cover of darkness. Gradually, by one method or another, a body of anatomical knowledge was accumulated.

Figure 2—Medicine in Art down the ages: a) An achondroplast, Chnoum-Hotep, as represented about 4600 years ago during the Egyptian 5th dynasty. Compare with, b) a dwarf, Don Sebastian de Morra, painted about 4000 years later by Velasquez. c) A poliomyelitis victim as depicted on a stele 3400 years ago, and d) An Etruscan statue of a posterior superior dislocation of the hip (c. 350 B.C.). e) An excellent mural painted about 2000 years ago depicting the wounded Aeneas. Compare with f) the rather stilted drawing in the Cambridge manuscript showing extraction of an arrow, made 1300 years later.

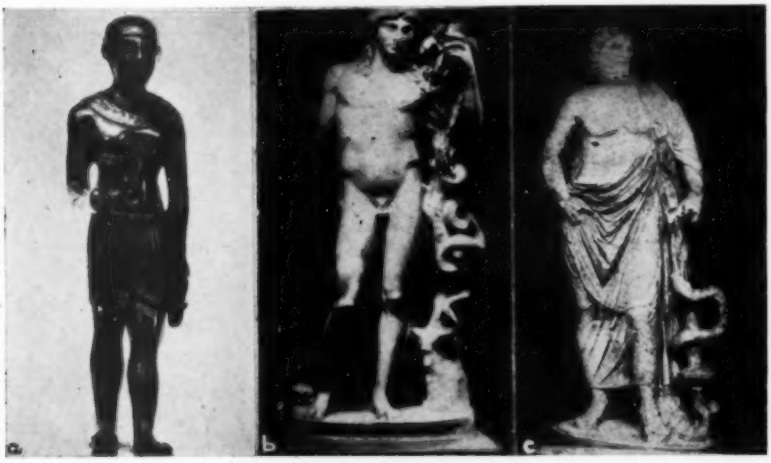

Figure 3—"Physicians" as depicted down the ages: Three medical divinities of antiquity; a) Imhotep was a priest, magician physician, artist and architect who lived about 5000 years ago. He was gradually elevated to a demigod and then to a full deity (god of medicine). Osler said that "he was the first figure of a physician to stand out clearly from the mists of antiquity." b) Apollon, the son of Zeus, was the god of beauty, music and song. To his oracles people turned in sickness, he is therefore represented as the father of Asklepios. c) Asklepios was actually a Thessalian king and the most renowned physician of his time. He later was deified. He stated that "it is the duty of a physician to cure his patient safely, swiftly and pleasantly." Compare the figures with modern concepts of physicians in Fig. 4.

It then became necessary to record and preserve these findings, and the union of medicine and art became a practical reality. Leonardo da Vinci made sketches of dissected human bodies and worked on a textbook of anatomy with the anatomist Marcantonio della Torre. The great Flemish physician and teacher Andreas Vesalius (Fig. 5) is perhaps the most notable example of the unity of artist and physician. Convinced of the inaccuracy of the classical anatomical drawings, Vesalius risked arrest and punishment to perform actual dissections and to record them in brilliantly executed and extremely accurate drawings. Preserved as woodcuts in Vesalius' *De Humani Corporis Fabrica* and *Epitome* (1543), these drawings mark a highpoint in the history of both medicine and art. A beautiful perspective view of Padua consti-

Figure 4—Physicians as depicted down the ages: More recent representation; a) The romantic point of view,—a painting by Jan Steel (1626-1679) of a physician taking the pulse of a love-sick maiden, b) the heroic attitude,—a painting by Rivoulon (1851) of a pioneer surgeon-urologist (Germain Colot), removing a bladder stone in the presence of King Louis XI in France in Jan. 1474. The patient is tied down, a priest stands nearby, and the locale is a cemetery. c) The satirical attitude,—medical consultation, a lithography by I. Boilly, (1761-1845). d) A rather coarse interpretation of Dr. Mayer Herman by Otto Dix of the modern school (1926). Compare with the idealized, idolized group in Fig. 3.

TABLE I.—SOME PHYSICIAN AUTHORS

ST. LUKE (First Century)	Third Gospel, New Testament
MOSES MAIMONIDES (1135-1204)	Philosopher, astronomer
SIR THOMAS BROWNE (1605-1682)	Philosopher, essayist
FRANCOIS RABELAIS (1490-1552)	Novelist
JOHN LOCKE (1632-1704)	Philosopher, essayist
TOBIAS SMOLLETT (1721-1771)	Novelist
OLIVER GOLDSMITH (1728-1774)	Novelist, poet
EUGENE SUE (1804-1857)	Novelist
OLIVER WENDELL HOLMES (1809-1894)	Essayist, poet
S. WEIR MITCHELL (1829-1914)	Novelist
SIR WILLIAM OSLER (1849-1919)	Essayist
SIR ARTHUR CONAN DOYLE (1859-1930)	Novelist
ANTON CHEKOV (1860-1894)	Novelist, dramatist
ARTHUR SCHNITZLER (1862-1931)	Novelist, dramatist, poet
W. SOMERSET MAUGHAM (1874-	Novelist
ALBERT SCHWEITZER (1875-	Essayist, biographer, historian, musicologist
WARWICK DEEPING (1877-	Novelist
A. J. CRONIN (1896-	Novelist
FRANK SLAUGHTER (1908-	Novelist
HANS ZINSSER (1878-1940)	Essayist
FRANCIS BRETT YOUNG (1884-	Novelist, poet, dramatist
THOMAS YOUNG (1773-1829)	One of the earliest Egyptologists

tutes the background in the anatomical plates–truly a combination of art and medicine.

The invention of the camera put an end to the need for realism in art. Revolutionary developments based on the new concept of *creative* art shook the venerable and complacent edifice of representational academic art. The *mind* as well as the eye and hand became important. The modern work of art became the conscious psycho-emotional reaction of the artist to his environment. Impressionism was followed by expressionism. These terms indicate that an artist now used his canvas to reveal fleeting *impressions* of a subject (Manet, Pissaro, etc.), or that he used it as a platform to express his *feelings* regarding that subject (Van Gogh, etc.). Developments in physics and spectrum dissection of light into its component colors led to pointillism (Seurat).

TABLE II.—SOME PHYSICIAN ARTISTS

ALEXANDER ANDERSON (1775-1870)	physician	first American wood engraver
SIR F. G. BANTING (1891-1941)	physician, physiologist (insulin)	painter
RICHARD BRIGHT (1789-1858)	physician, pathologist (nephritis)	painter
PIETER CAMPER (1722-1789)	anatomist	painter
HARVEY CUSHING (1869-1939)	neurosurgeon	painter
LEONARDO DA VINCI (1425-1519)	anatomist	master painter, sculptor, architect
ELISHA CULLEN DICK (1762-1825)	physician	painter (portrait of Washington)
SIR ALEXANDER FLEMING (1881-1955)	bacteriologist	painter
SIR FRANCIS SEYMOUR HADEN (1818-1910)	surgeon	founder and first president, Royal Society of Etchers
LEIGH H. HUNT (1784-1859)	physician	painter
CHEVALIER JACKSON (1865-	laryngologist	painter
S. WEIR MITCHELL (1829-1914)	surgeon	painter
E. L. TRUDEAU (1848-1915)	physician (Trudeau Sanitarium)	painter
ANDREAS VESALIUS (1514-1674)	anatomist	woodcuts (anatomical)
LEROY M. YALE (1841-1906)	physician	etcher, first president, New York Etching Society

Cutting into the structural heart of matter by planes, by radiography, helped to inspire cubism, abstractionism (Picasso, Braque, etc.) In futurism the artist attempted to dissect and depict motion,—a moving picture effect (Duchamp). The advances of medicine in psychology and psychiatry (Freud, etc.) led to non-objective improvisations (Kandinsky) and surrealistic Bridey Murphyisms (Klee, Miro, Chirico, etc.). Artists projected their minds into the canvas and tried to paint emotions, the unconscious, dreams, thoughts, complexes, infantile fixations, etc. It was inevitable that many artists and their products seemed to wander away from the masses who became perplexed by what seemed to them to be an unintelligible mumbo-jumbo by a mystery bearing hierarchy.

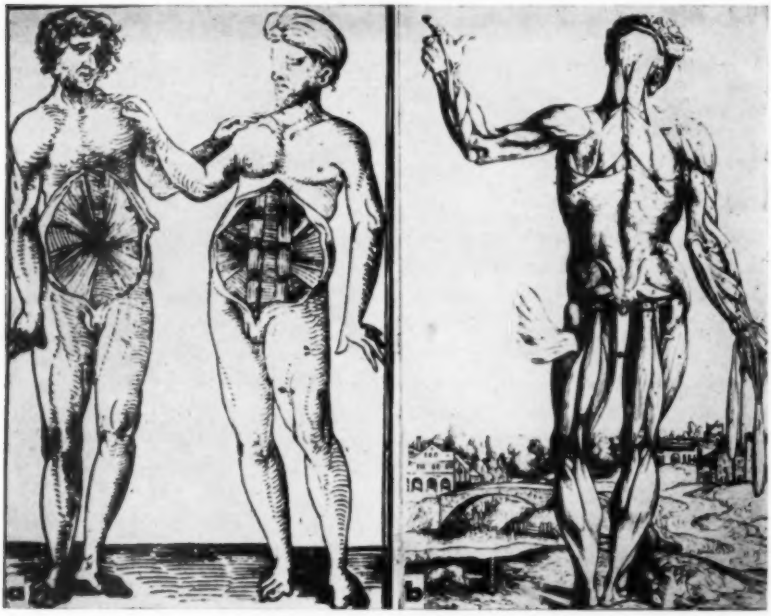

Figure 5—a) Anatomy before Vesalius;—a fanciful representation of abdominal musculature as depicted in the Methodus Anatomicus of Andres a Laguna, Paris 1535. Compare with, b) the relatively accurate and beautiful drawing by Vesalius (Xth plate of Muscles, Andreas Vesalius). Note interesting background (Padua), truly a combination of medicine and art.

Our era has seen the advent of a new phenomenon—the amateur artist. Never before have so many people been engaged in painting. Of all amateur painters doctors are perhaps the most devoted and in some instances the most skillful. It may be suggested that this fact is more apparent than real. To some extent the amateur art of physicians is given special publicity by the institutional self-consciousness exhibited in such groups as the American Physicians Art Association and the New York Physicians Art Club. Moreover, unlike the businessman who happens to be a Sunday painter, the doctor has a wider audience than his family and friends. A doctor may present informal exhibitions to his patients by filling his office and waiting room with his work,—and a patient in a waiting-room is a particularly vulnerable and intent

student of art. Finally, the activities of the medical profession have always had a special fascination for the whole body of laymen. People take a personal interest in all things medical. But the impression of doctors as particularly devoted amateur painters, from whatever source it is derived, does exist and is worth examining. Why do doctors paint? Essentially, for the same reasons that any amateur paints. They paint for pleasure; they paint for the delights of practicing a challenging and rewarding craft; above all they paint out of the need for an avocation. An avocation is a form, I suppose, of occupational therapy; it may relieve us simply from the demands and fatigue of everyday work, or it may help to repair the ravages of a serious illness followed by a long convalescence, or a grievous loss, or of a nervous disturbance. William Osler gave this advice: "No man is really happy or safe without a hobby, and it makes precious little difference what the outside interest be—botany, beetles or butterflies, roses, tulips or vases, fishing, mountaineering or antiquities—anything will do so long as he straddles a hobby and rides it hard."

It is true that doctors may have special reasons for painting. The medical student in the course of his training is likely to acquire a certain measure of artistic skill denied to the members of most other professions. From his first year of study he is required to record the materials presented to him in dissecting room and laboratory. He develops skills in line drawing, in the three dimensional representation of form and frequently in the mixing of colors. Indeed, he needs to develop these skills, for his mastery of his subjects to some extent depends upon them. During the difficult years of internship, residency and early professional practice most physicians forget this artistry. Many never recover it. In some, however, an interest in art is reawakened later, and these doctors begin their work as amateurs with a legacy of artistic training. Given aptitude or talent, the legacy may be put to good use. But, like all professional men, a physician has limited time for an avocation. He is aware that he can devote no more than his leisure hours to art, and that he may never develop to full stature in the medium he has selected. He therefore can let himself go. He is not subject to the stiffness and self-consciousness induced by unattainable goals. Because he need never apologize for his canvas, the amateur can do no wrong.

Finally, only an amateur can give tolerant approval to other amateurs, and completely unprejudiced appreciation to the masters' and

professional works of art. Knowing this, an amateur works in a kind of benign security from which no critic can dislocate him. All artists may be divided into three groups: that of the genius; that of the full-time professional, who is obligated to devote a lifetime to study and work; and that of the amateur, which anyone may enter, given a special combination of humility and courage. The paintings of one group must not be judged by the criteria of another, and tolerance seems to increase as we descend in the hierarchy. The amateur is in a position not only to appreciate the works of the genius and of the professional, but also to experience every now and then a bit of the excitement of creation that Vesalius, Rembrandt and Cezanne must have felt.

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MEDICAL ILLUSTRATION*

Its History, Significance and Practice

FRANK H. NETTER

As I have delved into the history of medical illustration and into the history of medicine I have been impressed with the important role which illustration has played in the advance of medicine and surgery to their present day magnificence. It is indeed striking to observe how through the ages men have been impelled to present their scientific concepts in the form of diagrams or drawings. And it is even more striking to realize the importance which these little marks on paper have had in the progress of medicine and surgery. It is true that at times medicine has seemed to move forward by sudden great leaps, then to remain fairly static until another great discovery came along.

I do not wish to detract from the glory of the great geniuses who have made these vital and far reaching discoveries in the past few decades; who have in fact almost revolutionized medical and surgical practice. But I think we must all realize that these great discoveries have been the culmination of the efforts of many men adding piece by piece, bit by bit to our knowledge in any given field until the last final discovery is made which clinches the entire subject. Thus our modern surgical and medical edifice has been built block by block by men who have added these stones one at a time in different times and in different parts of the world. This cooperative enterprise has been made possible through the dissemination of ideas, through the accurate depiction of one man's thinking, the accurate transmission of this man's thoughts to another man in a different part of the world and at a different time. The written word has served to a large purpose in accomplishing this but I believe that in the field of surgery illustrations have been even more vital. For it is only through a drawing that one can really transmit the concept of a procedure to one who is not actually present at the time.

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Medical illustration may be said to have three main functions: First it helps the student or physician who is studying a subject to clarify it in his own mind. As he sketches he is aided in forming a mental image of the subject. In this sense the hand cooperates with the brain. Second, it helps to transmit our ideas to others, as in a lecture, in a private conversation or in a conference or even in a published article. We transfer the mental image which we have via the paper to the mind of another. Third, it serves to preserve ideas for posterity—as in a book or any other publication. I would now like to call special attention to these last two categories in particular for it is by means of these two factors that I think the progress of surgery has been greatly aided through the medium of medical illustrations.

Men of all races and at all times and in all places have resorted to illustrations of one sort or another in putting down their ideas. The cave men cut into stone their ideas of what went on in the human body. The ancient Egyptians and Babylonians made crude medical illustrations. The American Indians in their primitive inimitable beautiful style did it. I have seen diagrams made by the American Indians telling the story of how an Indian ate some bad fish, how he got a fire in his belly and finally how he died. They actually drew a picture of a man with a fire in his belly and they had some concept of anatomy too, for they did indicate the intestines and some of the viscera. It is interesting to note their concept of fire as related to the origin of our term inflammation.

All through the middle ages very little was done in the field of medical illustration. Steeped in mysticism as those times were, medicine itself sank to a very low ebb and medical illustration along with all learning and all knowledge sank with it. Even Galen in the second century, though he contributed so much to medical knowledge, apparently did not indulge in or attempt to illustrate his prodigious writings. If he did there is certainly nothing left to us of his work in this field. I attribute this largely to the fact that there were no means in those days of printing or reproducing illustrations. Certain it is, however, that with the coming of the Renaissance, as all knowledge and medical science blossomed forth so also did medical illustration come into bloom.

At about this time, that is about the time that Columbus discovered America, Leonardo da Vinci was making his remarkable studies. If Leonardo was not the greatest genius of all time he certainly was one of the most versatile and universal.

Leonardo's essential characteristic was a fervent search for unity in all knowledge and all accomplishment. He studied and made contributions in practically every field of human endeavor, in science and in art. He was a great astronomer, geologist, engineer, physicist, philosopher, inventor, architect and, of course, painter and sculptor.

Noblemen called on him to build their palaces and fortifications, to make their statues and their monuments and to paint their ladies fair. He directed their pageants, built their canals. He designed cannons and devised the first tanks though he hated and condemned warfare. He was kind and gentle. Often he would buy birds just to set them free. He studied their flight and if he had had motive power at his disposal he most certainly would have invented a practical airplane. He did develop the practical submarine. He studied the winds and the air currents. He believed and taught that the earth revolved around the sun. He anticipated Newton's law of gravitation. He knew that the sea had at one time covered the land of Italy and that the folding of the earth's crust had countless eons ago raised up the mountains and plains above the sea level. I need scarcely touch on his painting for we know that he created two of the best known and probably best loved and certainly most valuable paintings of all time—the "Mona Lisa" and the "Last Supper."

Now as to Leonardo's studies and illustrations of anatomy, his work is all the more remarkable when we realize that he had no texts and practically no reference material of any kind. He had no *Gray's Anatomy*, no dissection manual to guide him. He had to create his own methods and techniques. In his lifetime Leonardo made approximately 30 dissections. It is amazing that under these circumstances this man obtained so sound a comprehension of the construction of the human body as his drawings reveal. Those of us who have done much dissection know how difficult it is even with a manual before us to trace out any system. And yet this man struggling under these most difficult conditions did accomplish so much. Worse still, he had to overcome the superstitions that had been built up through many ages.

There were two great characteristics to Leonardo's work: First, in this field as in others, he believed in basing his studies on facts rather than on authority. He said that if you find from your own experience that something is a fact and that it contradicts what some authority has written down then you must abandon the authority and base your reasoning on your own findings. He was much criticized for this because

many so-called wise men said that his ideas on anatomy could not possibly be so because some authority, some mysticus of the middle ages had written down out of his imaginings that things were quite different. But Leonardo cared little for the opinions of these people and he expressed his personal thoughts about them very pointedly in his own words as follows: "I care no more for the wind that issues from their mouths than I do for that which issues from their hind parts."

The second great characteristic of Leonardo's anatomical studies is that he was a functional anatomist. In this sense he had a really modern outlook on the subject. He sought constantly for the significance of anatomical facts. He has been called the founder of physiologic anatomy. For example, he made accurate and careful studies of the exact form and contour of the muscles but, not satisfied by this, he went further and represented them schematically as cords or strings because he said in this way one could get a better understanding of the direction of pull and of the action of the muscles.

The significance of this remarkable physio-anatomical approach in this man some five hundred years ago was forcibly brought home to me recently. When I was in Europe I visited some of the outstanding professors of anatomy. On two occasions, after being ushered with the proper ceremony into the sanctum-sanctorum of the good professors and after proper social greetings, I was told—"Dr. Netter we admire your pictures very much for their clarity and for their accuracy, in fact we are quite surprised at the detail and information that you have included but we do not understand why you mix up so much physiology and so much clinical medicine with your anatomy." I tried to explain that that was precisely what I was endeavoring to do—to give meaning and clinical significance to the morphologic facts I was depicting. But this they could not or would not understand. To them anatomy was a pure science. Theirs was the pure didactic approach. They awed their students simply by the force of memorized but useless facts. The professors in their ivory towers knew all the facts but they would not stoop to apply them.

The science of anatomy for many years suffered from this attitude. Some 30 or 40 years ago anatomy was a dead subject. All that could be known or that was to be known was already written down in the books. It simply remained to memorize books. To find any fact one simply had to turn to a certain page in any standard textbook of anatomy. But in

the last few decades there has been a new crop of anatomists who have returned to the physiologic and clinical approach. These men again ask why and what is the significance. As a result there has been a rebirth of interest in anatomy and today anatomy is again a living science. Investigators are turning to it more and more as a source for explaining phenomena. For example, the study of the spiral arteries of the endometrium has had much to do with developing the modern concepts of menstruation. Modern reparative surgery of the hand is based almost entirely on functional anatomy. Even our modern understanding of the function of the hypothalamus in regulating the activity of the pituitary and endocrine functions of the body has developed largely through the combined physiologic-anatomic studies of the neuro-humeral mechanism of the cells of the hypothalamus. Leonardo, with his inquiring mind, could not help but be a physiologic-anatomist.

Since Leonardo was an artist, many may have the impression that he studied chiefly surface anatomy. This was in general true of the other artist anatomists of the time, including such men as Michaelangelo, Raphael, Albrecht Dürer, etc. But Leonardo went much deeper. He studied the viscera, the nervous system, the circulatory system. He studied and drew the details of the larynx in order to gain an understanding of the production of the voice. He made drawings of comparative anatomy, comparing structures in animals to their counterparts in the human. He actually made injection preparations of the ventricles of the brain.

Leonardo's remarkable anatomical illustrations were not published in his lifetime. In fact at that time illustrated medical texts were nonexistent. Shortly thereafter, however, the idea of publishing anatomic plates began to take hold. Among the earliest were those of Charles Estienne, a Paris physician who collaborated with a surgeon, Riviere. Estienne employed a number of artists to make drawings but apparently he had difficulty in transmitting the idea to these artists that the purpose of the drawing was to elucidate anatomic facts not to create fanciful artistic monstrosities. At times the artists would get completely out of hand and run riot with the drawings. Often in illustrating a single anatomical detail, the artist would draw in the entire human figure and then embellish it with a decorative background or landscape until the essentials of the picture were all but lost. The drawings in general are rather crude but sometimes a little amusing as, for example, in an illustration

of the dura mater, the artist has drawn the entire figure in an active pose with the calvarium removed and hanging on a nearby tree as though the subject had just taken it off and hung it there as he would his hat. To Estienne, however, must be given the credit which is due a pioneer.

The great Andreas Vesalius established a landmark in the history of medical illustration. He has in fact been called the father of modern anatomy. Vesalius was born in Brussels in 1513 or 1514 of a family of physicians. He studied in France, traveled quite a bit, became court surgeon and finally professor of anatomy at Padua. His life was devoted to revolutionizing the teaching of anatomy and this he chose to do through the medium of published anatomic illustrations. He employed a number of artists to make drawings of his dissections but the man who probably made most of the illustrations was a brilliant pupil of the great painter, Titian, John Stephen of Calcar. It has been said that Titian, himself, made some of the drawings for Vesalius but most historians do not believe this to be true. Vesalius appears to have had considerable trouble with his artists; both with their temperament and with trying to get them to accurately depict the anatomy. Often the artist and anatomist berated each other heatedly. But when we realize that no preservative or embalming fluid was used in the specimens of those days we can scarcely blame the artists if they preferred to paint Madonnas rather than stinking carcasses. However, Vesalius always managed to get Stephen of Calcar back to work by offers of more money. It is amazing how artistic temperament succumbs to this commodity.

The works of Vesalius were far in advance of anything done up to that time, both in anatomic accuracy and artistic quality. The drawings are made with exquisite beauty and power and they reflect the high levels of art and learning of that time as well as the great calibre of the artists who made them. Much of their charm is derived from the graceful pose of the figures and from the lovely bits of landscape and background with which the artist embellished them. These background bits of artistic fancy, however, are never so dominant as to interfere with the clarity of the illustration. They may have served a useful purpose as well, for at that time it was considered proper to make anatomic studies for artistic purposes but it was somewhat frowned on when done in the name of medical science. Despite Vesalius' prodigious labors he never lost his love of travel and he finally died in a shipwreck in 1564.

A contemporary of Vesalius, namely, Giovanni Canano, also began

work on an atlas of anatomy about the same time but when he heard of Vesalius' superior undertaking he gave up the project and only completed a small volume on the upper extremities.

Vesalius really started something. The idea of illustrated anatomical and medical texts took hold and there followed a number of others. Vesalius' pictures were reproduced from woodcuts but soon thereafter many of the pictures were printed from copper or steel engravings. Some of the outstanding works were those of Eustachi, Varolio (on the brain), Casserio, Spigelius, Bartholinus, Santorini, L'Admiral and Scarpa. Many of these names are preserved to us today in our modern anatomical nomenclature. Thus we have the Eustachian tube, Santorini's duct, Spigelian lobe of the liver, Bartholin's gland and Scarpa's fascia.

William Hunter, the celebrated English physician and obstetrician of the 18th century, founded with his own money an institution for the study of anatomy. He employed a number of artists to make drawings most of which were studies of the gravid uterus. John Hunter, his distinguished surgeon brother, also helped in this project—particularly in the anatomical studies.

The next great step forward in medical illustration came with the invention of lithography, about 1800. Up to this time all the illustrations had been reproduced from woodcuts or from copper or steel engravings of one sort or another. This meant that the artist first had to make the drawing and an engraver then had to copy it and actually engrave or carve it into the wood, copper or steel. This was a tedious and expensive process. Much of the quality and accuracy of the original drawing was sometimes lost in the engraving and fine gradations of tone or shading were very difficult or impossible to reproduce. Lithography is a process of printing based on the mutual repulsion of oil and water. In the original lithographic process, the drawing was made on the stone with a grease crayon. The stone was then wet with water, but the water wet only the stone and not the greased areas. An oily ink was then applied and this in turn did not adhere to the wet stone but remained only on the crayon marks—the heavier the crayon the heavier the ink. The stone was now applied to the paper and a duplication of the drawing appeared. To reproduce colored illustrations a separate drawing was made on a separate stone for each color, the drawing of course being very carefully and accurately registered. Each stone was then printed in a different colored ink, one superimposed on the other. Through lithography a

number of beautiful and exquisitely illustrated anatomical, medical and surgical texts appeared in the 19th century. I cannot possibly enumerate them all but will mention a few. A beautiful and elaborate series of anatomic plates was published by Jones Quain about 1842. Another outstanding example was the surgical anatomy of Joseph MacLise published in 1851. The French seemed to have developed lithography to its highest artistry and the *Treatise on Fractures* by Anger and Velpeau published 1865 is an outstanding example. This beautiful volume, containing 100 lithographed plates in full color, is reproduced in exquisite fidelity and realism.

From what I have already said it is obvious that the development of medical illustration went hand in hand with improvements in the reproduction process. The final great advances in pictorial reproduction came with the invention of photoengraving in 1868, the halftone screen in 1880 and finally the four color printing process in 1893. These made it possible to reproduce pictures efficiently, accurately and economically by photomechanical means. It made possible the reproduction of practically any type of drawing in all gradations of tone and even in color—although color printing even today is costly.

In 1894 there came to this country from Germany an artist named Max Brodel. He was brought here largely through the influence of Dr. Howard Kelly and Dr. Thomas Cullen of Johns Hopkins Medical School and he voluminously illustrated many of Dr. Kelly's writings and also those of other famous Hopkins physicians. Brodel did much to advance the standards of medical illustration in this country and a school for medical illustration was founded at Hopkins under his direction. He developed what is known as the scratch board technique. In this technique a special clay-coated paper is used known as Ross board. The drawing is made with a black chalk dust applied with brushes and then blended to the desired shading. The highlights are then scratched out with a sharp instrument, giving a very luminous effect to the illustration.

Max Brodel and a number of his students made many beautiful and excellent drawings in this technique. Unfortunately, however, the technique became somewhat of a fetish and some artists who came after seemed to have gotten the notion that making a good medical illustration depended not on how well one depicted the subject matter but simply on using this technique. I do not mean to condemn this technique for I have used it myself and I believe that good and bad drawings can be

made in any medium. I simply wish to caution against permitting any technique to become more important than the drawing itself.

Another pioneer in American medical illustration is Tom Jones of Chicago. He illustrated the *Cross Section Anatomy* by Eycleshymer, Curtis' *Textbook of Gynecology* and many other works and he also founded a school for medical illustration at The University of Illinois. Jones employs a wash or water color technique and also works in pen and ink. A number of other schools for teaching medical illustration have since been started in various institutions throughout the country. The art of medical illustration has also been fostered through the employment of artists by various institutions and hospitals. It is unfortunate, however, that more funds are not available for this purpose today and that many of the large hospitals and even teaching institutions do not have medical artists on their staffs. Medical publishers also have become very picture conscious but unfortunately, they also do not make funds available so as to make it worth while for the artist to labor in this difficult but very important field.

I am often asked "How did you ever get the idea to go into the field of medical illustration instead of the actual practice of surgery?" The truth of the matter is that I never really got the idea and that I sort of fell into it gradually. I started out in life with every intention of being an artist and not a doctor. I studied at the National Academy of Design and at the Art Students League and actually did considerable commercial illustration, portrait work, scenic painting and worked professionally in many fields of art. But then I changed my mind and decided to be a doctor, fully believing that I was through with art for good. In medical school, however, I found that I could learn my subjects better by making drawings in my note books rather than by attempting to memorize the texts. As a result, my books were full of sketches. Some of my professors noted my drawings and asked me to illustrate their articles and books and this occupied most of my spare time in medical school and during my internship. On opening my office I again put away my art supplies intending to devote myself exclusively to surgery. But these were the days of the depression and there seemed to be more demand for my pictures than there was for my practice and the day finally came when I was so busy with pictures that it was necessary for me to make a choice between the two fields and, happily, I chose illustration. Since then I have worked on many very interesting projects. One of the most arduous of

these was building the transparent woman for the San Francisco World's Fair Golden Gate Exposition. This was a transparent figure of a woman seven feet high with a synchronized voice that told the story of the endocrines in the female. It depicted the menstrual process and the development and birth of a baby as well as the physical and sexual development of a woman. I labored on this project day and night for seven months. An interesting side light in my career was when I was commissioned to paint a series of 12 incidents in the life of a physician. This consisted of a series of large paintings of such subjects as the students sitting up the night before the osteology examination studying away to the point of exhaustion; the emergency ward; the ambulance call; the class reunion; the country night call, etc.

During the war I was in the Army stationed first at the Army Institute of Pathology and then at the Surgeon General's Office in charge of graphic training aids for the medical department. The Army soon learned the value of pictures in the saving of time in teaching medical and semi-medical subjects. Being an officer I was not supposed to make drawings myself and this was fortunate, for many of the projects which were assigned to me called for as many as a thousand or more illustrations. I would plan, roughly sketch and lay them out to be executed by others. We executed a number of manuals and portfolios on such subjects as first aid for combat troops, a roentgenology for technicians, sanitation in the field, survival in the tropics, etc.

After the war I devoted more and more of my efforts to work under the sponsorship of the Ciba Pharmaceutical Products Co. Several years ago I began, under the Ciba sponsorship, a monumental project illustrating the entire anatomy and pathology of the human body, system by system, and this project I expect will occupy the major part of what remains of my working career. Thus far two volumes have been published—*The Nervous System* and the *Reproductive System*. The *Digestive System*, because it is so voluminous, will be published in three parts: First, *The Liver, Gallbladder, Bile Ducts and Pancreas* which is now in press. Second, *The Alimentary Tract from Mouth through the Stomach*. Third, the remainder of the alimentary tract. From there on we will progress to the circulatory system, the endocrine system and so forth. I do not, however, expect to follow a purely systemic approach but will deviate from this occasionally to a regional one. For example, I expect to do a volume on the extremities and another on the head and neck.

Now as to how I work. I cannot give a sure-fire formula for making a successful medical illustration. I believe that each artist develops his own methods and technique but I will try to give a few basic principles and to tell a little how I, personally, make a drawing. First comes the study and this is the most difficult and unquestionably the most important part of the entire undertaking. I never start a drawing until I have a thorough grasp of the subject matter. When I say a thorough grasp I mean not just enough so that I can make a picture but so well that I feel perfectly at home in the field; so well that I understand the essential points, the points to emphasize and the points to eliminate. I must know just exactly what I am trying to express with this picture—what I am trying to say and what idea I am trying to transmit. This study is done in various ways. First of all come talks with the consultant. For each subject we try to choose a consultant who is outstanding in the field. This may mean trips to various parts of the country but they are worth the effort. Then I make intensive study of the published literature. At times, visits to hospitals are necessary to observe clinical cases, pathological or surgical specimens or operative procedures. Sometimes an original dissection is necessary. When I feel that I have thoroughly grasped the subject and can mentally visualize what I want to put on paper I proceed with the sketch, trying always to keep my original mental image from becoming befuddled. I make my sketch on a tissue or tracing pad, using cheap pencils both for economy and because I find that the points stand up better than do the expensive ones. Always keeping the fundamental idea of the picture in mind, I have found three basic considerations which are useful in planning a picture. These are, first of all—the point of view; that is, whether the subject is to be viewed from above, the side, the rear, etc. Second is the plane; that is, to what depth is this dissection to be carried. In some pictures two or three or four different planes of dissection may be necessary. For this reason I believe that the medical artist must be a good visualizer of anatomy. Finally there is the consideration of focus. By this I mean, how large an area is to be included in the illustration. Are we to draw in the entire body, half the body, or only a small area?

Having completed the sketch I now transfer it to a piece of illustration board for the finished drawing. I do this by blacking up the back of the picture with a soft pencil and then taping the tissue down on the illustration board with scotch tape and then going over the lines with a

hard pencil. I have used various media for my finished illustration over the years but I now work almost exclusively in what is known as opaque water color which is called in art terminology "gouache"—this means ordinary transparent water colors mixed with white paint. I hold no brief for this medium and I use it simply because I have found that I am more at home in it and that I can work more rapidly. In this field I believe that it is essential that the artist should feel at home in his medium for if he finds himself struggling with a medium or with the drawing he will not be able to concentrate adequately on the subject matter that he is trying to depict. As one works in a medium one learns many little tricks and devices which will help give certain effects.

Finally I should like to express my appreciation for the help and encouragement I have had over the years from Dr. Ernst Oppenheimer who has edited and continues to edit the Ciba volumes on which I am now at work. He has been a friend and counsellor who understood the problems with which I was confronted and helped me overcome them. We have often differed in our points of view, but these differences have been healthy and the resulting compromise has always been for the best. I am grateful indeed for having had this stimulating association.

BERNARD SUTRO OPPENHEIMER LECTURE

Dr. Dickinson W. Richards, Lambert Professor of Medicine, College of Physicians and Surgeons, Columbia University and Director of the First (Columbia) Medical Division, Bellevue Hospital, will deliver the first Dr. Bernard Sutro Oppenheimer Lecture on May 21, 1957 at 8:30 p.m. in Hosack Hall of The New York Academy of Medicine, 2 East 103 Street, New York City. The title of Dr. Richards' lecture will be "Some Problems in the Physiology of Dyspnea."

SECTION ON MICROBIOLOGY*

Abstracts of Papers

Presented at the Meeting, February 15, 1956, at The New York Academy of Medicine

The Role of Infection in Illness Following Exposure to Acute Total Body Irradiation

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INTRODUCTION

The subject of the part played by infection in illness and death following exposure to irradiation has received exhaustive treatment in recent papers and reviews.[1-5] However, it may be profitable at this time to consider the importance of infection in acute radiation illness, the etiology of increased susceptibility in these individuals, and the practical implications of these considerations to the physician in terms of the management and treatment of patients exposed to acute total body radiation. Infection is one of the few manifestations of acute radiation illness that can be effectively coped with by means of drugs in general clinical practice.

In the following discussions, acute whole body radiation in the sublethal and lethal ranges (from below the radiation dose that will kill no individuals within 60 days of exposure, to that range where all so exposed will die within this time period, in the absence of therapy) will be dealt with principally.[2] Most human beings that die do so in the third to the fifth week following exposure, with manifestations of infection and hemorrhage secondary mainly to bone marrow depression. This is the range of practical medical interest, where intelligent handling will save individuals who might otherwise die. As the radiation dose is increased, individuals die earlier, most within the first week. Death here is associated with severe fluid imbalance and shock probably secondary to the essentially complete denudation of villi of the small intestine.† Vigorous fluid therapy will tide over these individuals until the bowel regenerates (demonstrated in dogs by Conard, Cronkite, Brecher and Strome, report in preparation); however, they fall victim, with no exceptions, to the later sequelae of bone marrow damage. There is no known practical therapy for these sequelae at such high dose levels, and thus, under mass-casualty conditions, efforts might much better be spent on others who could benefit.

EVIDENCE OF THE PART PLAYED BY INFECTION IN RADIATION DAMAGE

Evidence that infection is of importance in the acute radiation syndrome falls into several categories: (a) clinical observations on human beings exposed to large doses of radiation in the Japanese bombings and in

* Maclyn McCarty, *Chairman*,
A. M. Pappenheimer, Jr., *Secretary*.

† The small bowel shows some early damage in the lethal range; however, the damage is not lethal and recovery is rapid.

reactor accidents, and similar observations on large animals dying from radiation exposure; (b) correlative studies on mortality rate, time of death, and incidence of positive blood cultures in animals; (c) challenge of irradiated animals with virulent and normally non-virulent organisms; (d) studies on germ-free animals; (e) studies of the effectiveness of antibiotics in reducing radiation mortality rate; (f) studies on the effectiveness of agents that will augment or restore natural anti-microbial defenses on mortality rate in irradiated animals. A brief word on each of these lines of evidence is given below:

The Japanese dying of "atombomben-disease" and human beings heavily exposed at the Los Alamos accident,[6] showed unmistakable evidence of infection. Signs and symptoms included high fever, Ludwig's angina and other mucosal and cutaneous infections, cellulitis, pneumonia and septicemia. Autopsy findings bore out the clinical picture. Similarly with large animals, particularly dogs, the temperature begins to rise three to four days before death, and is usually quite high prior to death. Orocutaneous lesions are common. At autopsy, pneumonia is the rule, as well as other evidence of infection.

At doses of total body radiation even in the high sublethal range, however (Marshallese exposed to fallout gamma radiation[7]) no evidence of increased susceptibility to infection may be manifest. This group of individuals, in some of whom the neutrophil counts fell below 1,000/c.mm., showed no increase in the incidence of infectious diseases over control groups. An epidemic of upper respiratory infection that occurred in the group was no more pronounced in extent or severity in the exposed population compared to control populations in which a similar epidemic occurred at the same time.

The time of peak incidence of bacteremia in irradiated animals has been correlated with the time of peak incidence of mortality in the extensive studies of Miller, Hammond and Tompkins.[8] The organisms are chiefly enteric in origin, and apparently gain access to the blood stream through the bowel wall. A positive correlation, of course, does not prove cause and effect, and it has been stated that such organisms represent agonal invasion and thus may be "incidental." A cause and effect relationship seems highly probable, however, particularly in the light of evidence from antibiotic therapy studies outlined below. Total body irradiation has been shown to activate infections that otherwise remained "latent."[9]

Challenge of irradiated animals with virulent, or normally non-virulent bacilli results in death at infective levels that produce no mortality in non-irradiated control animals. With virulent organisms, an appreciable increase in mortality rate is seen at x-radiation dose levels below those producing mortality in the absence of challenge.[10] With normally non-virulent organisms, the mortality rate following exposure in the lethal range is appreciably enhanced. Increased susceptibility to viruses, Rickettsia, parasites such as Trichinella spiralis, and bacterial toxins in the irradiated animal has been reported. A synergistic effect of x-radiation and cortisone in increasing susceptibility to administered bacteria and viruses has been reported.[11]

It is of importance to point out, however, that there is considerable variation in the degree of increased sensitivity to different microorganisms or toxins, and in the degree of effects depending on the route of administration (see under mechanisms of increased susceptibility below). Specifically, Hale and Stoner[12] have shown that although a marked increase in susceptibility to pneumococci is evident in the irradiated mouse, no such increase is found for mice challenged with a virulent influenza virus. With the virus inoculation, the animals were protected against secondary bacterial invasion with antibiotics. The degree to which the reported increased susceptibility to viruses in irradiated individuals is due to secondary bacterial invasion is not known. Some grounds for expecting such results are available. Neutrophils play a large role in resistance against bacterial, but not viral diseases.[13] The peripheral neutrophil count is profoundly affected by irradiation, and thus a greater degree of altered immunity to bacterial, rather than viral infections might be expected. At any rate, blanket statements

relating to susceptibility of the irradiated host are not warranted, and specific consideration in each instance must be given to the infecting agent, the host, the physiological state of the host and the degree of exposure to both radiation and the infectious agent.

Germ-free animals die following total body exposure to x-radiation.[14] The dose required to kill, however, is somewhat higher than for "normal" animals, and the survival time is increased. These results can be taken as indicating that infection may be responsible for death in the irradiated animals in certain dose ranges. At higher doses, animals die even in the absence of infection. Extensive hemorrhage probably is a major cause of death in such animals; however, undoubtedly other poorly understood biochemical changes contribute.

Antibiotics administered following radiation exposure have been shown definitely to enhance survival under some circumstances. The incidence of spontaneous mortality has been shown to be reduced, and mortality in x-irradiated mice subsequently challenged with virulent organisms has been decreased.

Results have not been uniformly encouraging, however, and completely negative results have been reported. Two human beings exposed in the Los Alamos reactor accidents died despite vigorous antibiotic therapy.[9] It is possible that improved results would be obtained with a schedule of administration designed to avoid the development of resistant bacteria.[15] Of significance in this regard is the recent report[16] showing that mice exposed to neutron radiation are protected from death by antibiotics during the first ten days, but not in the 11 to 30 day period when most mice die following x- or gamma radiation. This would indicate that under some conditions, at least, infection alone does not account for the mortality observed.

Thus, there is no doubt that infection contributes greatly to the disease process and mortality following exposure to total body radiation. However, it is equally clear that acute radiation illness is not an infectious disease in the usual sense; rather infection is a complication of a serious debilitating underlying disease which specifically interferes with defense mechanisms against bacterial invasion. Death may occur in some individuals, whether infection is present or not, at high dose levels. Thus antibiotics are not curative as with primarily infectious diseases, and dramatic cures cannot be expected from this type of therapy.

However, as with any debilitating disease, antibiotics definitely will prevent death in a certain number who might otherwise die, i.e., prevent death until regeneration and restoration of functions allow normal defense mechanisms to again protect the exposed individual.

MECHANISMS OF INCREASED SUSCEPTIBILITY TO INFECTION

Nearly all known body defenses against bacterial invasion have been reportedly impaired by large doses of total body radiation. *The skin and mucous membranes* normally provide an effective barrier to the invasion of bacteria. Following irradiation, however, small eroded areas, frequently secondary to hemorrhage, may appear. These lesions may destroy the effectiveness of the barrier and allow the entrance of bacteria. Such ulcerations are found on the skin, and most frequently on the mucous membranes of the tonsil, mouth, and large bowel.

Considerable discussion has centered about the bowel as the portal of entry, particularly for the enteric organisms found in blood cultures of severely exposed individuals. There seems little doubt that the agranulocytic ulcerations, frequently precipitated by hemorrhage, do provide portals of entry. It has been shown in mice that the number of bacteria which normally get across the intestine in small numbers and are trapped in the regional lymph nodes does not increase following total body irradiation during the early phase when damage to the small intestine is maximal. The liver and spleen, however, become infected with enteric microorganisms before the blood stream is invaded.[17] It appears, therefore, that the fatal bacteremias which develop in mice are not the result of the primary early gut damage, but of the impairment of the animals' defenses against enteric bacteria that normally invade from the bowel lumen. The

phagocytic cells are able to clear the blood of bacteria for only a few days. It has been suggested that the defect in bacterial removal is related to the leukopenia since cross circulation in rats, and thus the addition of viable leukocytes capable of active phagocytism, corrected the defect.[18] The type of bacteria recovered in blood cultures varies from species to species, and it would be particularly dangerous to extrapolate such results directly to man. There is no doubt that the combination of total-body radiation and additional trauma may result in death when either entity separately would not have proved fatal.[19, 20] With large area burns, deaths may occur early, presumably from shock. With smaller burns or lower radiation dose, however, deaths appear later and appear to be the result of infection. It is logical to incriminate the superimposed burn as a portal of entry. The organisms found in the bacteremia produced in dogs given thermal burns in addition to radiation were the same as those found locally in the thermal burn.[21] Antibiotics have been shown to prevent these later deaths from combined thermal and radiation injury.[21]

The lymphatic spread of injected virulent organisms has been shown to be accelerated following total body radiation.[22] The lymph nodes which normally arrested the progress of infection were no longer able to perform this function. This failure presumably resulted from the inability to mobilize neutrophils in the nodal sinuses, a process necessary for the efficient filtering out of bacteria by the nodes.[23] A similar mechanism has been postulated to explain the increased susceptibility of cortisone-treated animals to bacterial infection.[23] There is relative scarcity of leukocytes at the site of experimental infection following cortisone administration. This accelerated spread of the infecting bacilli results in rapid bacteremia. Thus the injection of virulent bacteria[2, 22] results in infection and death in the irradiated animal much more rapidly than does inoculation by natural means such as inhalation.[10]

Depression of the peripheral white cell count, particularly the neutrophil count, is considered the cardinal reason for increased susceptibility to infection and death from infection in the irradiated individual. The time to maximum depression is longer in man than in animals.[7] Clinically, and in large and small animals, evidence of infection is not seen until the neutrophil count reaches low levels, usually 1000/c.mm. or less. In mice given a mid-lethal dose of x-radiation, in extensive experiments, an excellent correlation was obtained between survival and the neutrophil count taken four or seven days after irradiation.[24] No such correlation was obtained from the lymphocyte count. A similar correlation was obtained in irradiated mice challenged with Pseudomonas, whether recovery from the damaging effects of radiation proceeded at a normal rate or was accelerated by spleen homogenate treatment.[25] Therapy that will restore or accelerate restoration of the bone marrow and thus of the peripheral neutrophil count is of value in acute radiation injury.

Studies on the importance of neutrophils in radiation infection and mortality are correlative in nature for the most part, and do not prove cause and effect. Evidence that some factor in addition to neutrophils is of importance is seen in the recent studies of Miller and his group (personal communication from C. P. Miller) in which mice made markedly leukopenic by low-dose-rate irradiation did not show the marked increase in susceptibility to a challenge inoculation observed in mice in which similar levels of leukopenia were induced with acute irradiation.

The effects of radiation on the *phagocytic activity* of fixed and wandering macrophages have received attention. Irradiation has been reported to alter the rate and extent of migration of white blood cells, and the indices of phagocytosis.[26] Studies have been reported on the inhibiting effect of radiation on the *bactericidal activity of serum*.[27, 28] The degree of importance of these reported changes in post-irradiation infection is not clear. *Antibody production* is known to be markedly impaired, a subject which Dr. Dixon will cover.

IMPLICATIONS FOR MANAGEMENT OF IRRADIATED INDIVIDUALS

The results of animal experimentation obviously cannot be carried directly to

human beings. However, in the light of experience with both animal and human exposure to acute total body radiation, the following recommendations with regard to the management of acute total body radiation illness, insofar as infection is concerned, appear justified.

At sublethal levels, the only evidence of exposure may be laboratory—decreased blood count. The lymphocytes fall within hours; the neutrophils do not reach maximum depression until the fifth or sixth week. The disease is like any clinical granulopenia, and symptoms do not occur until the neutrophil counts become very low and infection appears. If the patient can be carefully observed, no treatment other than careful observation is necessary. Bed rest is not necessarily indicated, nor are prophylactic antibiotics. These agents are necessary, in general, only if the clinical condition would indicate them had the individual received no irradiation. Prophylactic antibiotics should be considered, however, if the patient has sustained additional trauma, or if careful observation is not possible (catastrophe conditions). Broad-spectrum intensive therapy should be used, if any is employed, because of the possible development of drug-fast organisms.

The principles of therapy outlined for sublethal exposure pertain in general to the lethal range as well. Good hygiene, nursing care and nutrition should be maintained. Conditions that arise should be treated on an individual basis. Antibiotics in general should be given only as indicated, and not prophylactically. The use of any drugs without undoubted indication is discouraged because of their unknown and possibly harmful effects on the irradiated individual whose metabolism is deranged. Parenteral administration of drugs should be held to a minimum because of the added trauma in an individual susceptible to purpura and infection. At present there are no specific prophylactic or therapeutic agents, other than antibiotics, that should be stock-piled for use in the hematological depression resulting from radiation exposure.

A program of active immunization should be carried out prior to the time of possible exposure. Burns and wounds in the irradiated individual should be debrided and cleansed as soon after exposure as possible, and primary closure should be accomplished wherever possible. Healing of even major surgical wounds apparently is not appreciably impaired under these circumstances,[9] and tensile strength is not markedly affected. It appears likely that surgery several days after heavy exposure would not be as well tolerated, and that the possibility of increased mortality from infection, as with added thermal trauma, might be increased. The apparent synergism between irradiation and cortisone administration in increasing susceptibility to infection[11] should be kept in mind in therapeutic considerations. The relatively late fall in neutrophils in human beings, as opposed to most animals, following irradiation should be kept in mind.

Experimental prophylaxis and therapy of radiation damage in animals have received considerable attention. A wide variety of compounds that protect, if present in the tissues *during* irradiation, have been reported. Success has also been attained with fresh preparation of hematopoietic tissues (bone marrow, spleen). None of these, however, is of practical value as yet in the treatment of human radiation exposure.

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The Effects of Radiation on Immune Processes

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The most significant observations made during studies of the effects of radiation on immunity include: inhibition of primary antibody response when radiation precedes antigen; enhancement of primary antibody response to certain antigens when radiation is given shortly after antigen; radioresistance of the secondary response to some antigens; and protection of the immune response of radiated animals by shielding organs such as spleen or appendix from radiation. Inhibition of the antibody response by whole body radiation preceding antigen was first demonstrated shortly after the turn of the century and has been confirmed by a large number of workers employing a wide variety of host-antigen systems. Our observations employing heterologous serum protein antigens in rabbits are more or less typical of these studies and can serve as an example. The amount of radiation necessary to inhibit the antibody response is relatively small and makes few changes in most biologic systems. As little as 75 r, 250 K.V. whole body radiation given two days prior to antigen seems to cause some decrease in the antibody response and 125 r causes a marked inhibition. Two hundred r almost completely suppresses the response and no detectable antibody appeared following doses of 300 and 400 r. In addition to inhibiting antibody synthesis,

doses of 100-200 r produce morphologic changes in lymphoid tissues and bone marrow, and perhaps gonads, but most of the other tissues are not appreciably altered. This parallel in radiosensitivity between the antibody response and lymphoid tissue has been an important part of the evidence for lymphocyte participation in the antibody response. Regardless of the specific role of the lymphocyte, these observations indicate that either extremely radiosensitive cells, or radiosensitive processes in otherwise resistant cells, perform an essential function in the primary antibody response.

The importance of the time relationship between radiation and administration of antigen was noted by the early workers and recently has been more completely studied. Again, I will use data obtained in our laboratory to illustrate this work. Employing as a model the primary response of rabbits to heterologous serum proteins, it was found that, while 400 r given two days before antigen would completely suppress the immune response, the same dose of radiation given 12 hrs. prior to antigen was less effective and when given five hours prior to antigen resulted in only 50 per cent suppression. When radiation and antigen were given simultaneously, a response equal to 75 per cent of that in unirradiated control rabbits followed. Four hundred r given six hours after antigen had little effect on antibody production and 800 r, a LD_{50}, given three days after antigen delayed slightly but did not diminish the antibody response. From these observations, three conclusions may be drawn: First, it appears that an essential step occurring early in the primary antibody response is dependent upon something which is lost following 200-400 r whole body x-radiation. The time necessary for loss of this x-ray sensitive material after 400 r exposure is between 12 and 24 hours. Second, since radiation given simultaneously with antigen only slightly suppresses the antibody response, it follows that this essential step in the primary response which is dependent upon the radiosensitive material takes place within about 12 hours after injection of antigen. Third, the remainder of the antibody response is radioresistant and can proceed in spite of severe radiation injury to all tissues and near extinction of lymphoid tissues. On the basis of these observations one can divide the primary immune response into an early radiosensitive phase lasting only a few hours and during which the initial handling of antigen and any adjustment of host to antigen must take place and a second radioresistant phase during which antibody synthesis takes place.

While the foregoing observations appear to hold for all host-antigen systems tested, enhancement of the antibody response by radiation has been described only under particular circumstances. Agglutinin and hemolysin responses have been increased although sometimes delayed by radiation when radiation was given shortly after the antigen. Similar enhancement of the precipitin response to soluble antigens has not been observed. One possible explanation for the enhancement of the response to particulate antigens might be that the balance between the competing processes which on the one hand prepare the antigens for effective stimulation and on the other sequester and degrade the antigen tending to eliminate it as an immunologic stimulus, could well be shifted in favor of the former by radiation given soon after antigen. It has been demonstrated that the non-specific phagocytic and digestive functions of the reticuloendothelial system are adversely affected by radiation and this change might well increase the effectiveness of a given dose of antigen. The recent report of enhancement of the immune response to bovine serum albumin by doses of meningococcal endotoxin, which among other effects do suppress reticuloendothelial activity, lends some support to this postulation. The course of the effect of radiation on the immune response therefore, goes through a period of enhancement with some antigens when radiation is given just after the antigen and then a period of depression when the radiation precedes the antigen. The duration of this depression is one or more months, depending upon the antigen-host systems and dose of radiation.

Another interesting effect of radiation was observed in the case of secondary antibody responses to heterologous serum proteins and foreign red blood cells. The secondary response of rabbits to soluble

protein antigens proved to be quite radioresistant, being only slightly delayed by 800 r given two days prior to secondary challenge. In contrast the secondary response of rabbits to a variety of particulate antigens proved to be equally as sensitive as the primary response to radiation given before the antigen. Here again, it seems most likely that the difference between these two kinds of responses is dependent upon the difference between antigens. The response to soluble protein antigens is probably less complicated than the response to bacillary or red blood cell antigens because of the phagocytosis, digestion, etc., involved in the case of the particulate antigens. If some orientation of cells toward antigen persists after the primary response, the secondary response to protein antigens would merely involve direct stimulation of antibody synthesis by the soluble antigen. Since antibody synthesis has already been found to be quite radioresistant one might expect the secondary response to soluble antigens also to be radioresistant. In the case of the response to particulate antigens, on the other hand, there is an essential step in both primary and secondary responses which is prevented by previous radiation. Since it seems likely that the persistence of orientation of host to antigen and the radioresistance of antibody synthesis should hold in the secondary response to particulate antigens as well as to soluble antigens, the difference must be in the manner in which the body initially handles the antigens. It is possible that there is a step in the preparation of the particulate antigens by the host which is essential for both primary and secondary responses and which is prevented by radiation prior to administration of antigen.

Finally, I would like to take up the work demonstrating that shielding of certain organs, usually those rich in lymphoid tissue, during otherwise whole body irradiation protects the immune response. This protective effect of shielding has been presumed by Jacobson and associates to be mediated by a humoral factor liberated by the shielded tissue which promotes recovery of the host's tissues. However, on the basis of recent observations with transplanted rather than shielded tissues, it seems more likely that this protection is due directly to the shielded cells which repopulate the injured tissues of the host. In the case of the protection of the immune response by shielding spleen or appendix during radiation, the latter explanation is certainly adequate. The amount of lymphoid tissue involved in the usual experimental immunologic response has been shown by cell transfer work to be much less than can be found in the above mentioned shielded tissues so that the shielded cells themselves could easily account for the responses observed.

By way of summary let us review the various steps in the immune response in the light of these radiation experiments. In the primary response, the initial handling of particulate antigens by the host appears to be greatly influenced by radiation. Radiation given shortly after antigen appears to increase the efficiency of the particulate antigen perhaps by interfering with the non-specific degradation of the antigen. Little or no effect of radiation on the handling of soluble protein antigens or the antibody response to them has been demonstrated. The adaptation of host to antigen is apparently a brief process lasting 12 hours or less and is dependent upon some substance or situation which is lost or destroyed within 12-24 hours after 300 r x-radiation. Once initiated, the process of antibody synthesis appears to be resistant even to doses of radiation in the lethal range. In the secondary response it was found that the preparation of particulate antigens by the host was a radiosensitive process which made the secondary response to these antigens equally as radiosensitive as the primary response. In the case of soluble protein antigens there were apparently no radiosensitive elements in the secondary response.

SECTION ON MICROBIOLOGY*

Abstract of Paper

Presented at the Meeting, November 28, 1956 at The New York Academy of Medicine

Adenovirus Respiratory Disease and Its Control by Vaccination

M. R. HILLEMAN

Chief, Department of Respiratory Diseases, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

The acute respiratory illnesses caused by viruses of the Adenovirus (RI-APC-ARD) family are a major medical problem to the Armed Forces. Clinical illnesses caused by these agents include undifferentiated acute respiratory diseases (ARD), non-Streptococcal exudative pharyngitis, atypical pneumonia and pharyngoconjunctival fever. Such illnesses are known more commonly as grippe, catarrhal fever, virus pneumonia, acute pharyngitis or severe colds. Although there are at least 14 known serological types of Adenovirus, only 3 of these, types 3, 4, and 7, have been found important in military populations. Respiratory disease caused by these agents occurs in recruits during all seasons of the year, but is most prevalent in the winter months when 9 of every 10 hospital cases of respiratory illness may be of Adenovirus etiology. On a yearly average, 1 of every 10 recruits who trains at Fort Dix, N. J., a typical training base in a northern climate, is hospitalized for 8 days for respiratory illness caused by these agents. This effects great losses in the cost for hospital care, reduction in man-power, lowered operating efficiency, and the consequences of disruption of the troop-training program, especially in time of war.

The serious effect of Adenovirus disease in the Armed Forces made it imperative to develop a safe and effective vaccine against these agents. A formalin-killed Adenovirus vaccine prepared from infected monkey kidney tissue cultures has been developed in our laboratory at the Walter Reed Army Institute of Research. The vaccine is bivalent and contains types 4 and 7 virus, the predominant military types. A single 1 ml. dose of the vaccine induces in human volunteers neutralizing antibody levels against homologous types 4 and 7 virus and against heterologous type 3 agent which are as great as ordinarily reached following the natural disease.

A controlled field evaluation of the vaccine effectiveness was carried out among the recruits in 6 training companies at Fort Dix, N. J. during the winter of 1956. The study included 311 vaccinated soldiers and 313 receiving a formalin-saline placebo for control purpose. The vaccine was highly effective in preventing acute respiratory illness of Adenovirus etiology, beginning 1 week post-vaccination. After this time, 61 serologically positive hospital cases of Adenovirus disease occurred among the 313 controls while only 1 case occurred among the 311 persons given the vaccine. Thus, there was a 98% reduction in the expected number of hospitalized Adenovirus cases. Additionally, indirect serological evidence suggested a reduction also in mild Adenovirus cases requiring only outpatient care and in inapparent infections. No evidence was obtained relative to the duration of protection.

The vaccine caused no untoward effect in the persons who received it and it is completely safe for human use. The vaccine is of great potential value in military populations but its need in civilian groups remains to be determined.

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SURGERY OF CONGENITAL HEART DISEASE—Robert E. Gross, *Surgeon-in-Chief, The Children's Medical Center, Boston, Mass.*

May 16 — STEROID HORMONE PRODUCTION AND METABOLISM IN MAN—Thomas F. Gallagher, *Member of Sloan-Kettering Institute for Cancer Research, New York City.*

May 23 — CHEMISTRY IN MENTAL DISEASE—Paul H. Hoch, *Commissioner of Mental Hygiene, State of New York*

May 30 — THE NATURE OF DRUGS WITH MENTAL ACTIONS AND THEIR RELATION TO CEREBRAL FUNCTION—M. Ralph Kaufman, *Director, Department of Psychiatry, The Mount Sinai Hospital, New York City*

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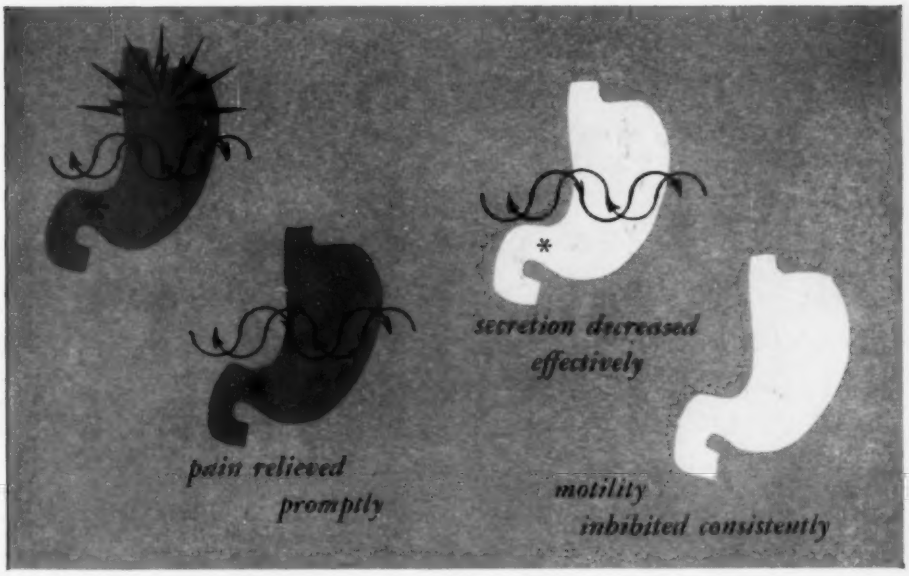

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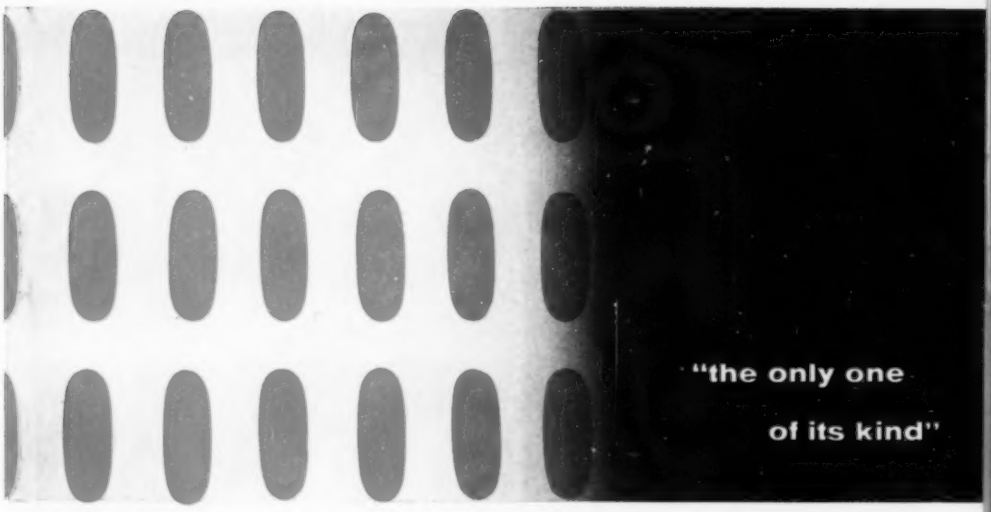

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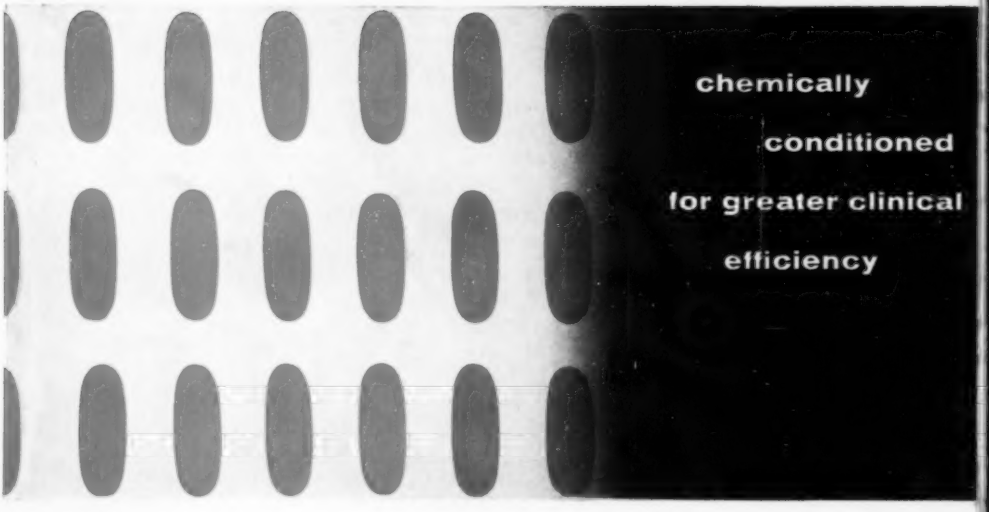

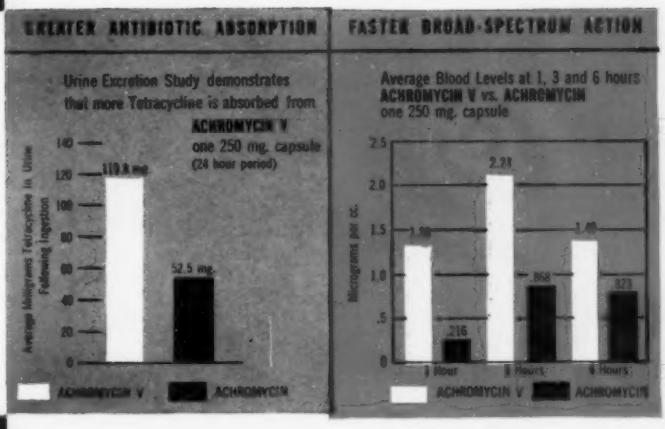

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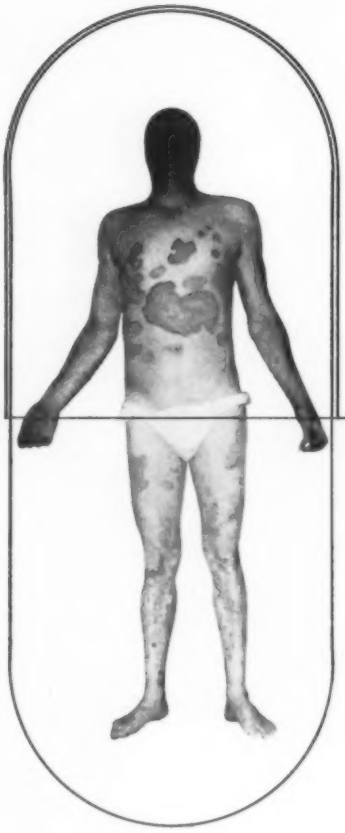

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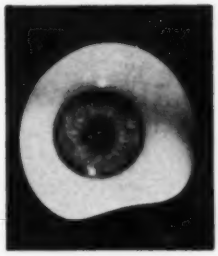

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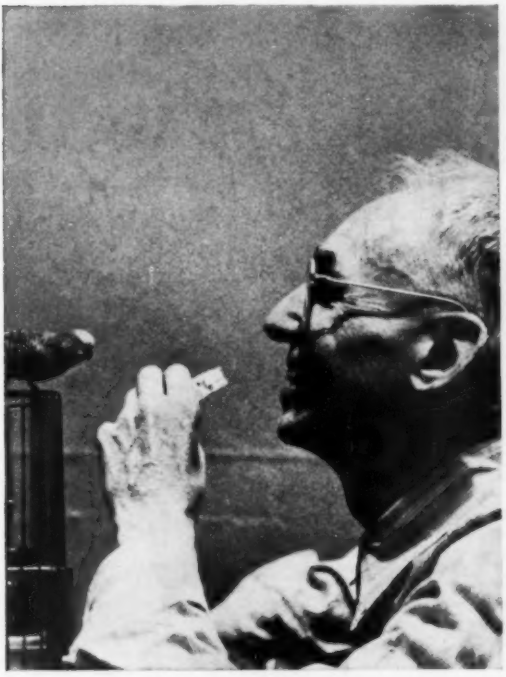

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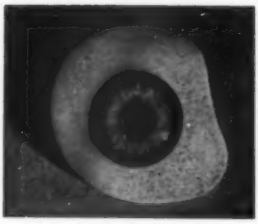

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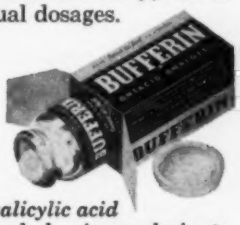

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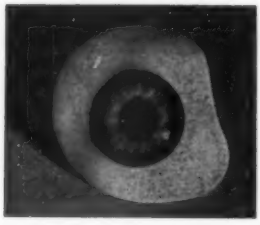

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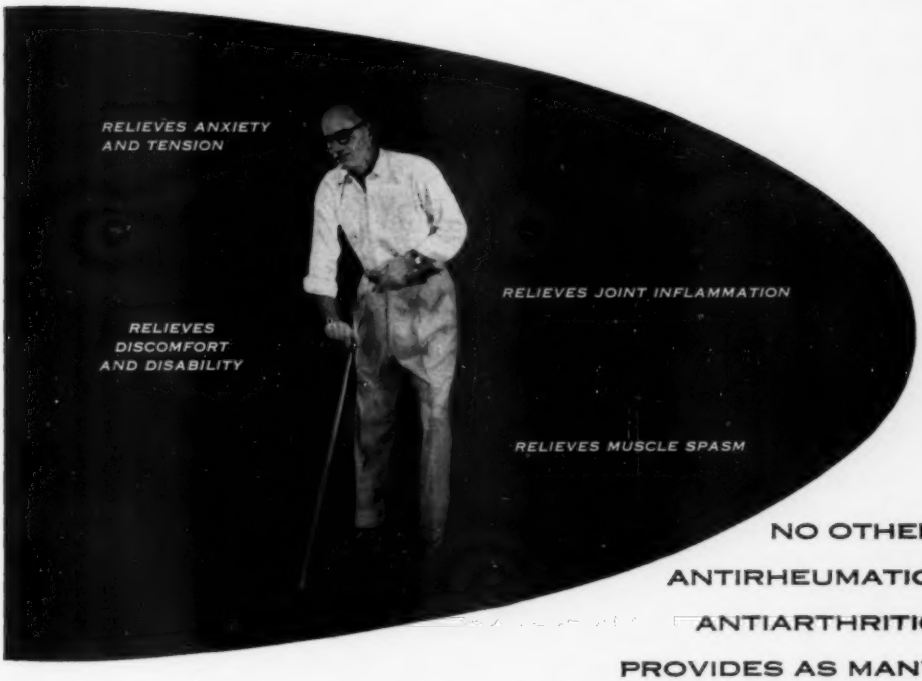

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